IN THE DISTRICT COURT OF CLEVELAND COUNTY
STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel., MIKE HUNTER, ATTORNEY GENERAL OF OKLAHOMA,	**Case No. CJ-2017-816**
Plaintiff,	**Judge Thad Balkman**
vs.	**William C. Hetherington**
	Special Discovery Master
(1) PURDUE PHARMA L.P.;	
(2) PURDUE PHARMA, INC.;	
(3) THE PURDUE FREDERICK COMPANY;	
(4) TEVA PHARMACEUTICALS USA, INC.;	
(5) CEPHALON, INC.;	
(6) JOHNSON & JOHNSON;	
(7) JANSSEN PHARMACEUTICALS, INC;	
(8) ORTHO-MCNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS;	
(9) JANSSEN PHARMACEUTICA, INC., n/k/a JANSSEN PHARMACEUTICALS, INC.;	
(10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.;	
(11) WATSON LABORATORIES, INC.;	
(12) ACTAVIS LLC; and	
(13) ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC.,	
Defendants.	

PLAINTIFF'S THIRD MOTION TO COMPEL DISCOVERY AND BRIEF IN SUPPORT

Plaintiff, the State of Oklahoma (the "State") files this Third Motion to Compel Discovery ("Motion") from Defendants Cephalon, Inc. and Teva Pharmaceuticals USA, Inc., (the "Cephalon Defendants"), pursuant to 12 OKLA. STAT. §3237, and respectfully shows the Court the following in support.

I. INTRODUCTION

As the State alleges in its petition, this case is about a massive and unprecedented conspiracy amongst all Defendants to increase the sales of opioids by changing the way doctors viewed and prescribed opioids generally. Pet. at ¶¶ 58-71. In addition to marketing their own branded drugs (*i.e.*, Oxycontin®, Actiq®, Fentora®), the Defendants conspired to destigmatize and promote opioids as an overall ***class*** of drugs to encourage doctors to prescribe opioids more liberally—increasing overall prescriptions and sales of Defendants' opioids: both *branded* and *generic. Id.*

In December, Judge Balkman denied Defendants' Motions to Dismiss, confirming the sufficiency of the State's claims. Thus, the issue of whether generic opioids are relevant to this case has already been ruled on. Nevertheless, Cephalon Defendants refuse to produce *any* discovery related to their generic opioids.

Cephalon Defendants do not dispute, nor can they, that they funded and collaborated with members of the medical community and third-party organizations that spread pro-opioid messaging. Instead, Cephalon Defendants simply ignore the State's claims—and Judge Balkman's Order— and contend that "this case is about marketing" and because they didn't market or promote their *generic* drugs specifically (*e.g.*, Teva's generic form of OxyContin - oxycodone

hydrochloride), no discovery related to their generic opioids is relevant or will be produced in this case.

Defendants' position ignores that its efforts to promote opioids as a ***class*** of drugs (also referred to as unbranded marketing) led to increased prescriptions in ***both*** generic and branded opioids. Huge profits resulted from these efforts, as did the present addiction crisis. Generic opioids are just as much a part of this epidemic as their branded counterparts. Thus, discovery related to generic opioids is highly relevant and critical to the State's claims in this case.

Accordingly, the State asks the Court to overrule the Cephalon Defendants' relevance objection. To the extent the Cephalon Defendants are withholding any information or documents based on this objection, the information and documents must be produced.

II. BACKGROUND

The State sent its first set interrogatories to the Cephalon Defendants on August 3, 2017. Through the Cephalon Defendants' objections and subsequent meet-and-confers, the State learned that the Cephalon Defendants refused to produce *any* discovery in this case related to their generic opioids. As an example, the State's Interrogatory No. 2 asked the Cephalon Defendants to "State the amounts of gross revenue and net profits earned by You from the sale of Opioids in Oklahoma." The following is an excerpt from an April 4, 2018 meet and confer:

> **MR. DUCK:** So the question for us, and I hope that we haven't in some way been unclear on this, but the question for us is not whether your clients marketed generic opioids. The question and the discovery we're trying to get at is the sale of and the presence of your clients' generic opioids in the State of Oklahoma, and it sounds like to me – and please correct me if I'm wrong -- but it sounds like to me you're saying that your view is that ***no discovery related to your clients' generic opioids is relevant or will be produced in this case. Is that accurate?***
>
> **MR. BARTLE:** ***Correct. I mean, I don't know how it's relevant if you – if you claim that this is a case about frauds and misrepresentation in marketing,***

> ***which is what the claims are, if our client didn't do any of those things with regard to generics, I don't see how that's relevant to this case."***

Exhibit A, April 4, 2018 meet and confer transcript at 24:5-22 (emphasis added).

At the April 19 discovery hearing, the Cephalon Defendants' counsel reiterated their position stating that:

> **MR. MERKLEY:** Neither company has ever promoted or marketed generics. Cephalon has never even manufactured generics, much less promoted them. While Teva manufactures generics, it's never marketed or promoted; thus generics simply aren't relevant to the State's asserted claims . . ..

Exhibit B, April 19, 2018 hearing transcript at 100:21-101:1.

The State now brings this motion to compel.

III. LEGAL STANDARD

Courts liberally construe the Discovery Code to provide the just, speedy and inexpensive determination of every action. 12 OKLA. STAT. §3225. "Parties may obtain discovery regarding any matter, not privileged, which is relevant to the subject matter involved in the pending action, whether it relates to the claim or defense of the party seeking discovery or to the claim or defense of any other party." *Id.* at §3226(B)(1). When a party fails to completely respond to discovery requests or produce materials "as requested," the requesting party "may apply for an order compelling discovery." *Id.* at §3237(A).

IV. ARGUMENT

Just because the Cephalon Defendants never promoted or marketed their own specific generic drugs does **NOT** mean that they never promoted or marketed opioids generally. Indeed, as shown below, the Cephalon Defendants went to great lengths to promote opioids generally to shift the way in which doctors and patients think about pain and, specifically, to encourage broader use of opioids.

The Cephalon Defendants' self-serving position ignores the State's allegations. More importantly, it ignores the role the Cephalon Defendants played in what public health officials have called the worst drug crisis in American history. For the Cephalon Defendants to claim that their generic opioids are not relevant to this case is to ignore every Oklahoman whose life has been ruined by addiction simply because they took generic opioids rather than branded opioids.

The Cephalon Defendants spent millions of dollars to promote opioids generally as a ***class*** of drugs. These efforts were not limited to branded opioids. They were intended to—and did—result in an increase in prescriptions and sales of both *branded* and *generic* opioids. Thus, generic opioids are just as much a part of this epidemic—and this case—as their branded counterparts.

A. The Cephalon Defendants' Unbranded Marketing Efforts Promoted Widespread Use of Opioids Generally

As the State alleges in its petition, Defendants created this epidemic, in part, by sponsoring pro-opioid front groups, funding articles and Continuing Medical Education ("CME") classes on general opioid use, and paying physicians thousands of dollars every year to publicly opine that opioids were safe, effective and non-addictive for a wide variety of uses. Pet. at ¶¶ 58-71. These efforts are often referred to as "unbranded marketing" because they were not brand-specific. Rather they aimed to change the way the medical community, and the public, viewed opioids overall. They deliberately conceived these strategies to create, and in fact did create, an entirely new "health care" narrative – one which claimed pain was seriously under-treated throughout the U.S. and opioids were underprescribed.

For example, through its sponsorship of the Federation of State Medical Board's "Responsible Opioid Prescribing: A Physician's Guide" the Cephalon Defendants, along with other opioid manufacturers, encouraged the more liberal prescribing of opioid medication. The

guide's clear purpose was to focus prescribers on the purported undertreatment of pain and falsely assure them that opioid therapy is an appropriate treatment for chronic, non-cancer pain:

- Opioid therapy to relieve pain and improve function is a legitimate medical practice for acute and chronic pain of both cancer and non-cancer origins;
- Patients should not be denied opioid medications except in light of clear evidence that such medications are harmful to the patient

These messages were not limited to Defendants' ***branded*** opioids. The guide, sponsored by the Defendants and their pain foundations, became the seminal authority on opioid prescribing generally for the medical profession and dramatically overstated the safety and efficacy of opioids and understated the risk of opioid addiction.

Further, the Cephalon Defendants also sponsored the journal Advances in Pain Management. In an issue published in 2008, there are multiple articles from various Key Opinion Leaders including Dr. Russell Portenoy, Dr. Steven Passik, Dr. Kenneth L. Kirsh and Dr. Lynn R. Webster, all advancing the safety and efficacy of opioids. Exhibit C. In an article titled, "Appropriate Prescribing of Opioids and Associated Risk Minimization," Drs. Passik and Kirsh state: "[c]hronic pain, currently experienced by approximately 75 million Americans, is becoming one of the biggest public health problems in the US." *Id.* at 9. They assert that addiction is rare, that "[m]ost pain specialists have prescribed opioids for long periods of time with success demonstrated by an improvement in function" and that then-recent work had shown "that opioids do have efficacy for subsets of patients who can remain on them long term and have very little risk of addiction." *Id.* at 10.

Just recently, in a report titled "Fueling an Epidemic: Exposing the Financial Ties Between Opioid Manufacturers and Third-Party Advocacy Groups" United States Senator Claire McCaskill of Missouri exposed these clandestine promotional efforts and described how manufacturers,

including the Cephalon Defendants, contributed to advocacy groups and doctors tied to them, who then amplified industry messages supporting the use of the painkillers generally.[1] Senator McCaskill noted:

> The fact that these same manufacturers provided millions of dollars to the groups described below suggest, at the very least, a direct link between corporate donations and the advancement of opioids-friendly messaging. By aligning medical culture with industry goals in this way, the groups described in this report may have played a significant role in creating the necessary conditions for the U.S. opioids epidemic.

The Senator later added in a statement that "[t]hese financial relationships were insidious, lacked transparency, and are one of many factors that have resulted in arguably the most deadly drug epidemic in American history." It is worth noting here that Senator McCaskill commented that the Teva Defendants did not cooperate with her investigation and stonewalled many of her requests for information just as they are doing here.

These are just a few examples of Defendants' promotional efforts to dramatically expand ***overall*** opioid prescriptions which led to this epidemic, efforts which were wildly successful.

V. CONCLUSION

This case is not just about *branded* opioids. This epidemic is not just about *branded* opioids. The Cephalon Defendants' position that they never marketed or promoted generic opioids is simply false and should be ignored. As explained above, they spent millions of dollars to change the way opioids were perceived and prescribed in this country—and it worked.

For these reasons, the Cephalon Defendants' information related to generic opioids is highly relevant to this case. Respectfully, the State now asks the Court to overrule the Cephalon Defendants' relevance objection. To the extent the Cephalon Defendants are withholding any

[1] *See* Exhibit K to the State's March 8 Status Report at 11-12.

information or documents based on this objection, the information and documents must be produced.

Dated: April 27, 2018

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I certify that a true and correct copy of the above and foregoing was mailed and emailed on April 27, 2018 to:

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STATE OF OKLAHOMA, ex rel., MIKE HUNTER, ATTORNEY GENERAL OF OKLAHOMA,	)	
Plaintiff,	)	Case No. CJ-2017-816 Judge Thad Balkman
vs.	)	Special Master: William Hetherington
PURDUE PHARMA L.P., et al.,	)	
Defendants.	)	

DISCOVERY CONFERENCE BETWEEN THE PARTIES
(Teva and Cephalon Defendants)
April 4, 2018
(Via Telecommunications)

DISCOVERY CONFERENCE BETWEEN THE PARTIES, taken in the above-styled and numbered cause on April 4, 2018, from 10:05 a.m. to 10:44 a.m., before WILLIAM M. FREDERICKS, CSR in and for the State of Texas, reported by machine shorthand at the offices of Nix Patterson & Roach, LLP, 3600 North Capital of Texas Highway, Suite B350, Austin, Texas.

Job No. 2861870
Pages 1 - 31

A

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MR. PATE: Let's go ahead and go on the record.

All right. This is Drew Pate with Nix Patterson. We're here to have a meet and confer about Teva -- the Teva and Cephalon Defendants' Answers and Objections to the Plaintiff's First Set of Interrogatories. We've got Brad Beckworth, Trey Duck, Cody Hill and Ross Leonoudakis on the phone for the Plaintiff.

Harvey, do you guys want to go ahead and enter your appearances now that we're on the record.

MR. BARTLE: Sure. This is Harvey Bartle on behalf the Teva Defendants. We have Evan Jacobs, Richard Shephard and Megan Braden from Morgan Lewis on the phone, as well as Nick Merkley from Gable Gotwals.

MR. PATE: Okay. Thank you. And based on the judge's ruling at the last hearing, our understanding is that you guys then -- or someone on your team is the decision-maker for the issues that we're going to discuss today?

MR. BARTLE: Correct.

MR. PATE: Okay. Who would that be?

MR. BARTLE: That's going to be me, Harvey Bartle.

MR. PATE: All right. Okay. Great. Thanks, Harvey.

MR. BARTLE: And what about on your end, Drew?

MR. BECKWORTH: Brad Beckworth is here, Trey Duck, Drew Pate.

MR. BARTLE: Which one is the decision-maker? Is it just -- all three of you or just one?

MR. BECKWORTH: The three I just listed, as I said in open court as well. Obviously, probably like you guys, there are issues we have to get client approval on, but for that I think we're all decision-makers on any issues that are relevant.

MR. BARTLE: Great.

MR. PATE: Okay. Great. Well, let's get started then. The easiest way to start is just probably going to be to walk through each interrogatory where Teva stated that they want to meet and confer before providing any information, and so let's just start with Interrogatory No. 1.

You state in your answer that you're willing to discuss the production of pertinent organizational charts that may contain information sufficient to identify persons.

Do you all have a proposal or a response that you intend to provide?

MR. JACOBS: Yeah. So I -- we are --

THE REPORTER: Who is this, please?

MR. JACOBS: Sorry. This is Evan Jacobs.

We are willing to provide our organizational charts. I believe we have them going back to about mid-2007, and we think most of the pertinent players will be able to be identified through that.

In addition, we plan on providing you with the -- with our call activity files, which we've previously discussed, which will identify the sales reps who were in Oklahoma.

MR. PATE: Okay. Thank you. Are there any aspects of this interrogatory that you're not responding to or any information about people that right now you are withholding based on an objection?

MR. BARTLE: Well, Drew -- this is Harvey Bartle -- I mean, we still have an unresolved objection on time and geographic scope that is before Judge Hetherington, so we maintain the objection based upon that.

MR. PATE: Okay. Understood. And just

so we're clear, you're treating -- is there any additional information -- let me figure out the best way to say this.

Your objection with respect to RFPs on time and scope, you're applying that the same to your interrogatory answers; is that fair.

MR. BARTLE: Correct. Correct.

MR. PATE: Do you know when you're going to be producing the organizational charts?

MR. SHEPHARD: This is Richard. We will produce that information on our next production, which should be in the next couple of weeks.

MR. PATE: All right. Interrogatory No. 2 where we requested you to state the amounts of gross revenue and net profits earned by you from the sale of opioids in Oklahoma. As far as we can tell, you're just objecting to this interrogatory and not providing any response, so can you explain your position.

Hello?

MR. BARTLE: Oh, I'm sorry. This is Harvey. Our answer to this is we've been working on obtaining this information, but we don't have it by Oklahoma. So we're trying to figure out -- we're trying to see if we can obtain it.

MR. PATE: Okay. So you're not objecting to producing it; you're just looking into what you have?

MR. BARTLE: Yeah, we're trying to obtain it --

MR. PATE: Okay.

MR. BARTLE: -- if it exists.

MR. PATE: Okay. What -- as far as you know or -- what can you tell us today about what revenue and profits information you do have?

MR. BARTLE: Well, I'm not sure we can go into great detail on it, but we certainly don't have it specifically by state.

MR. PATE: Do you have it by -- go ahead.

MR. BARTLE: It's -- I don't know. We probably have it nationally, but presently not by state.

MR. PATE: Do you have it by -- and I'm just trying to figure out, you know, the best way to get at this answer. I understand you're still looking into it and appreciate that and would ask that you get back to us as soon as you know more, but just from what you know now, are there any sort of, you know, geographic region numbers or anything like that even

if not narrowed to a specific state?

MR. BARTLE: Rich, can you handle this. Is there any other information that we would have?

MR. SHEPHARD: And this is Richard. To our knowledge, we don't have it broken down by any geographic region, whether that be state or by area of the country. We're looking into whether or not there is a way to identify whether the information can be segregated as such, and we'll get back to you if we find out that that is the case.

MR. PATE: Okay. And this kind of relates to another interrogatory that we'll get to, but it might be helpful here.

Does Teva track sales numbers from, you know, like the sales rep team or group that's responsible for a particular state like Oklahoma and what they bring in?

MR. SHEPHARD: Well, it's difficult -- and this is Richard again -- to track the actual sales number because then you have to tie back the dollar value associated with a prescription, but what we do know Teva was able to track were the number of prescriptions by doctors based off of IMS data, which is obviously a third-party company.

MR. PATE: Do you know when you will

have more information about what information is available or what you can provide for this rog?

MR. SHEPHARD: We'll touch base in a few weeks with an update as to what we found and what information we've been able to glean from the company.

MR. PATE: Did you say in a few weeks?

MR. SHEPHARD: Correct. We'll touch base with you on that with an update.

MR. PATE: In the meantime can you provide the national-level numbers so we have something to work with?

MR. BARTLE: Yeah, I think that's -- there's the client involved in national numbers, Drew -- this is Harvey -- and our objection is based on scope and, you know, time, geographic scope and time. We still maintain that, and we don't believe it's relevant to this case, and obviously Judge Hetherington will decide that shortly.

MR. PATE: Okay. All right. Moving on then to the next interrogatory for identification of front groups. Again, you guys say you want to -- you're willing to discuss the production of documents containing information related to funding, so what do you want to discuss?

MR. BARTLE: Rich, can you identify what

we're going to be producing in response to this.

MR. SHEPHARD: Absolutely. This is Rich again. We're going to produce the documents related to the front groups and other organizations that you identified in rog 3 to the extent Teva has them in their possession, custody or control, and that will be able to show you the groups that Teva provided some sort of funding to related to the opioid products at hand.

MR. PATE: I think this is clear. I just want to make sure. When you say "Teva," you mean the entire Teva family of Teva, Cephalon, acquired Actavis, right?

MR. SHEPHARD: Correct. Those five entities to the extent that the documents exist with one of those entities or their subs.

MR. PATE: Are there any sort of reports that would be included like aggregate reports that show, you know, the amounts that Teva contributed to these organizations, or are the documents you're describing, you know, something else, like the actual company specific documents or front group specific documents?

MR. SHEPHARD: Well, the documents will include the actual grant requests from the outside

entity which went through the proper channels within the company. So those documents will provide that information, but we're also going to try to get together to the extent it is in the company's possession, custody and control an Excel spreadsheet that has the individual payments, which you then could aggregate on your end if you wanted to per organization or entity.

MR. PATE: All right. And just so it's clear what our position is, you know, we have a defined term for "front group," which we provide a definition of what we mean by that, and then also list several organizations that we know of.

To the extent Teva knows of others, you know, we expect that information to be included because Teva knows that better than we do. So I just want to make clear that our request isn't limited to like say, for example, the eight named front groups that we list in that definition.

MR. SHEPHARD: We understand that.

MR. PATE: Okay.

MR. HILL: So, guys -- this is Cody Hill at Nix -- just to be clear then, and maybe I missed it, after what Drew just said, you know, the larger group is what is intended by the question, and the

documents you're planning to produce would encompass more than just the eight identified groups or what you're planning to produce is limited to those groups?

MR. SHEPHARD: We are planning to look for all of the relevant organizations, which would potentially expand beyond the eight that are actually listed. So we're not limiting our search to just the eight that are listed.

MR. HILL: Okay. This is Cody. Thank you.

MR. SHEPHARD: No problem.

MR. PATE: Okay. No. 4, it looks like your answer is similar to No. 1, so maybe we can short-circuit this, but about identifying former sales reps, sales managers and medical liaisons, is that going to be included in the organizational charts that you intend to provide?

MR. SHEPHARD: Yes, it will.

MR. PATE: Is there going to be a way to identify former from current?

MR. SHEPHARD: If they no longer appear on the organizational chart, then they probably are going to be a former employee, meaning that they no longer work with the company.

MR. PATE: Meaning you're going to

provide like annual -- I'm just trying to understand. So there will be like annual organizational charts, and you're saying if someone fell off and is no longer present that's how we're going to identify a former?

MR. SHEPHARD: That is correct. The way the organizational charts are designed, they are created for the most part monthly or every other month, and then you will see if an individual is no longer on the organizational chart.

As far as the sales reps, which is one of the categories enumerated in the request, that you can more easily identify based on the call activity reports.

MR. PATE: What about medical liaisons?

MR. SHEPHARD: They will be in the organizational charts.

MR. PATE: Okay.

MR. HILL: This is Cody Hill again. So just to make sure I understand, if someone has fallen off, you know, and no longer on an updated list, is it fair to assume your firm is not representing that person? Do you follow me?

If somebody is no longer on a -- on one of the later charts and therefore appears to be a former employee, should we take that to mean that your

firm doesn't represent them?

MR. BARTLE: No, we -- we would take the position that we represent, you know, employees, present employees and former employees as it relates to their employment at Teva. So we're certainly happy to facilitate any service with regard to those people, or contact.

MR. PATE: Any former employee that's ever worked for Teva, you're saying you're -- just so I'm understanding -- you're representing all of them?

MR. BARTLE: Well, at it relates to this case, yeah.

MR. DUCK: Your position is that you would just rather us contact you first rather than reaching out to them first, because I don't think you can make a decision for a former employee about who their attorney is going to be? And we're fine with that. I --

MR. BARTLE: Well, I think that's right.

MR. DUCK: I get it. But you're not saying affirmatively that right now you represent all former employees?

MR. BARTLE: No. I think that's correct.

MR. DUCK: Okay. Thank you.

MR. PATE: Okay. No. 5. It's a similar one. You say you want to discuss the production of documents or a list. What's your proposal here?

MR. SHEPHARD: And this is Richard again. In our last production, which was on February 14th, we produced a spreadsheet which listed all the CMEs and IMEs occurring in Oklahoma or remotely going back to 2012, and we will continue to produce the relevant information related to CMEs, IMEs in Oklahoma or remotely.

MR. PATE: Okay. So that one is subject to your geographic scope objection until we get a ruling from the Court on that?

MR. SHEPHARD: That is correct.

MR. PATE: Okay. No. 6. We asked to state the amount of bonuses paid to sales reps, sales managers or other individuals selling opioids in Oklahoma and identifying the individuals who got the bonuses.

Are you planning on answering this interrogatory, or what's your proposal?

MR. SHEPHARD: We will provide you with spreadsheets listing each sales representative and manager in Oklahoma and the amount of bonus that they were paid at various times throughout the relevant

time period.

MR. PATE: All right. When do you plan on producing that?

MR. SHEPARD: We plan to have that ready for you in about six weeks.

MR. PATE: Is that -- are the sales reps and sales managers going to be I assume folks who were focused on opioid sales?

MR. SHEPHARD: Correct. These will be individuals that were responsible for the sales of Actiq and Fentora.

MR. PATE: All right. Moving on to No. 7 then for identification of KOLs, is this like No. 3 for front groups? Are you all planning on similarly responding?

MR. SHEPHARD: This one is similar -- and this is Richard again -- but there are some slight deviations. Because KOLs are HCPs that received payments, we'll provide you with a separate spreadsheet that lists all of the HCPs that received payments that are from Oklahoma.

And I know previously we had a discussion as to whether or not we would limit that to thousand dollar payments or more, but we are obviously willing to provide the data for all HCPs and all

payments to those HCPs in Oklahoma.

MR. PATE: The ones in Oklahoma?

So how do you identify someone in Oklahoma?

MR. SHEPHARD: That's where they're licensed to practice medicine. That is their address of record.

MR. PATE: All right. Will that spreadsheet include information about what they were paid for?

MR. SHEPHARD: Yes, it should.

MR. PATE: Do you know when you intend to provide that spreadsheet?

MR. SHEPHARD: That will most likely be in the second production that's that upcoming, which will be in about six weeks.

MR. PATE: All right. The next interrogatory is No. 8. Is this the same list that you're referring to here where we asked to identify all healthcare professionals in Oklahoma to whom you all sent sales reps or marketing information?

MR. SHEPHARD: And this is Richard again. In our last production, which was in February of this past -- of this year, we provided sales call activity logs for the sales representatives that

detailed Actiq and Fentora from 2006 up until the present, so you would already have the list of HCPs in which the sales representatives went and detailed Actiq or Fentora.

We are also working to see what other information may have been disseminated, and then once we identify that be able provide you with comparable Excel spreadsheets with that information as well.

MR. PATE: Okay. So you're still looking into the written marketing material side of it?

MR. SHEPHARD: Well, it's more or less the educational materials concerning opioids and/or pain treatment.

MR. PATE: Okay.

MR. SHEPHARD: The marketing materials would have been disseminated through the sales representatives who are listed on the call activity file reports.

MR. PATE: Okay. Skipping ahead to No. 12, does the list identifying -- that you're going to produce -- well, maybe you can just tell me which list you're saying would be responsive to this interrogatory. You describe a list in your answer.

MR. SHEPHARD: What we've already

provided is the call activity file, and on the call activity file there will be a column that will indicate the individual that was detailed during that sales call. So you will actually receive the name of the doctor that the detail was intended for.

MR. PATE: Does it list the institution, though, where the doctor -- like the doctor's office or in this case if they were at a medical school?

MR. SHEPHARD: It more likely than not does not have the individual institution listed for it because the actual call was to an individual doctor just to make sure that the doctor was being detailed and not somebody who should not have been detailed.

MR. PATE: Did Teva ever send sales reps just to medical schools to give out information or presentations like to students?

MR. SHEPHARD: That is something that we can look into and provide you with an answer if we find out whether that is or is not the case.

MR. PATE: Okay. Yeah, I'd appreciate it. You know, to the extent it's not included on a call log, if Teva calls it -- Teva or Cephalon, you know, if they call it something different -- you know, that's why we asked the question about sales reps or presenters. Anyone sent to a medical school giving

out information about opioids, that's what we want to know.

MR. SHEPHARD: Understood.

MR. PATE: Okay. Interrogatory No. 13, what's your proposal for --

MR. SHEPHARD: This is Rich again.

MR. PATE: Go ahead.

MR. SHEPHARD: We are working to obtain this information and produce it to you.

MR. PATE: Are there any objections that you all have that you're standing on for this one separate from the time period and the geographic scope?

MR. SHEPHARD: Of course -- right. Of course geographic scope, as well as the relevant time period.

MR. PATE: Nothing else, though, at this time?

MR. SHEPHARD: To the extent that we identify anything that is responsive, we will provide that information other than the two categories that I've already listed.

MR. PATE: Okay. Do you have any timeframe on this one?

MR. SHEPHARD: We are in the process of

obtaining the information, and we hope that we can possibly get it into a production to you in the six-week timeframe, but realistically that might not necessarily be feasible.

MR. PATE: Okay. Guys, this is Drew. Those are all the questions that I have today and that I think our side has today. I know we've got --

MR. DUCK: Hold on, guys. Just one second.

(Discussion off the record.)

MR. DUCK: Hi, everyone. This is Trey. I'd like to go back to rog No. 2, because there's something I realized that we didn't address there.

We want to be clear -- you know, you all saw the letter that we sent to the Court, and it's my understanding you're going to be responding to that today. I want to be clear that when we're talking about Teva's opioids and any revenue related to the sale of these opioids in Oklahoma, that includes generics.

So, you know, have you all done anything to look into that aspect of things or are you intending to produce information related to the sale of generic opioids in Oklahoma?

MR. BARTLE: We are not.

MR. DUCK: Why is that?

MR. BARTLE: This is Harvey. Because Teva didn't acquire Cephalon until 2011, and it never promoted or marketed or did anything with regard to opioids prior to 2011 --

MR. DUCK: And this case --

MR. BARTLE: -- with regard to generics. Never promoted them.

MR. DUCK: And this case includes --

MR. BARTLE: (Inaudible.)

THE REPORTER: I'm sorry. I can't hear you.

MR. BARTLE: Sure. It didn't promote them. It didn't market; it didn't promote; it didn't fund KOLs. It just manufactured generics.

MR. PATE: Did Teva sell generic form opioids in Oklahoma?

MR. BARTLE: Well, whether or not it sold generic opioids in Oklahoma is not -- the claims are about fraud and misrepresentation. The fact that it sold is actually, frankly, irrelevant because it didn't make any misrepresentations or market or promote its products.

MR. DUCK: Well, obviously we disagree on that, Harvey. I mean, you know, part of the case

is that the fraud that occurred occurred through unbranded marketing and the delivery of a message related to opioids generally. Generic opioids would fall into that category.

The fact that there was no specific generic marketing -- I mean, you know, generics are by their definition unbranded. So unbranded marketing is what we're talking about here. It comes as a surprise to us I think that you all are taking the position that no discovery will be had on generic opioids that have been manufactured for your client since 2011. Is that what you say? We view that as highly relevant.

MR. BARTLE: No. I'm saying prior to 2011 -- prior to 2011, Teva did not market or promote its generic opioids.

MR. PATE: Has it done so after 2011? I just want to make sure I'm understanding what the 2011 --

MR. BARTLE: Because Teva's involvement with Cephalon began in 2011. Cephalon never had generics. So Cephalon didn't do generics prior to 2011.

MR. PATE: Right. Just --

MR. BARTLE: Teva --

MR. PATE: Go ahead.

MR. BARTLE: -- had generics prior to 2011 and did not market or promote. So they didn't market or promote prior to 2011, and they don't market or promote generics now.

MR. DUCK: So the question for us, and I hope that we haven't in some way been unclear on this, but the question for us is not whether your clients marketed generic opioids. The question and the discovery we're trying to get at is the sale of and the presence of your clients' generic opioids in the State of Oklahoma, and it sounds like to me -- and please correct me if I'm wrong -- but it sounds like to me you're saying that your view is that no discovery related to your clients' generic opioids is relevant or will be produced in this case.

Is that accurate?

MR. BARTLE: Correct. I mean, I don't know how it's relevant if you -- if you claim that this is a case about frauds and misrepresentation in marketing, which is what the claims are, if our client didn't do any of those things with regard to generics, I don't see how that's relevant to this case.

MR. DUCK: You know, I don't know if it's a great use of our time to argue about that -- I'm not sure I'll convince you -- but our view of our

case is different than your view, and it is that your clients and the other Defendants worked together to change the perception of opioids generally in the medical community and thereby increase the number of prescriptions and sales of opioids. Generics are included in that.

You know, that's our position, and that's the way we see the lawsuit, and we think everything that we have submitted to the Court in all the briefing has been clear on what our position is with respect to unbranded marketing and the Defendants' intent to disseminate messaging, false messaging about opioids as a class of drugs generally.

That's our position, and I'm not asking you to agree with our position. I just need to know whether you're standing on your position that you're not going to produce any discovery related to generic opioids.

MR. PATE: I'm standing on our objection.

MR. DUCK: Thank you. Okay. I don't think that we have anything else.

MR. BARTLE: Do you guys have a sense of -- this is Harvey. Do you guys have a sense of when you're going to start producing documents?

MR. DUCK: We have a sense. I can't give you a date certain right now. Where we are in the process is we're reviewing documents for privilege and continuing to gather documents from relevant custodians. I think we've identified or come close to identifying all of the relevant custodians, but we're just right in the thick of it right now, Harvey, pulling all these documents and reviewing them for privilege on our side. So it's imminent. We're going to get you all stuff on a rolling basis hopefully starting in the next few weeks.

MR. BARTLE: Are you going to provide a list of the custodians that you chose?

MR. DUCK: Yeah, it's something that we'll consider doing. I haven't had a conversation with the various agencies at issue on that, but I can. I don't see any reason why --

MR. BARTLE: Okay.

MR. DUCK: -- we would, you know, have a categorical objection to doing that, but let me speak to everybody and we'll let you know.

MR. BARTLE: Well, I think it just makes sense. I mean, obviously we had sent you guys 10, you know, custodians. You asked for us to add two. We'll do that. You know, to the extent that we may

want to add additional people, we would hope that we could have a -- you know, a productive discussion of the adding of additional custodians.

MR. DUCK: Right. And you know, that brings up another thing. I don't know -- we're kind of learning right now for the first time that you all have not viewed your clients' involvement in this case as relating to the generics.

Did your selection of custodians in any way -- was that informed by that view? Are there additional custodians that would be included if the Court ordered that generics were a part of this case?

MR. BARTLE: Well, with regard to sales reps, you know, again, we don't have sales reps for generic opioids.

MR. DUCK: Well, sure.

MR. BARTLE: So it's a whole different matter. We don't promote them, like I said. So, you know, I don't know -- our custodians are related to Actiq and Fentora because they relate to what you asked about, which is marketing and promotion of those specific opioids, and, you know, that's what our custodians have been limited to.

MR. DUCK: Okay. Well, again, we think we've asked for more than that. That's helpful. I

guess we'll just cross that bridge when we get to it.

You know, at the hearing the other day when you mentioned to the Court that there were only, you know, 245, or whatever the number was, prescriptions for the -- the branded drugs, I assume that the reason you didn't mention the generics was -- in that same hearing was that you all have a view that those aren't part of this case?

MR. BARTLE: Well, we do have that view, but that's not the reason why. That comes from your complaint, or your petition.

MR. DUCK: So why didn't you --

MR. BARTLE: And that has to do with the discovery scope.

MR. DUCK: Why didn't you discuss the numbers about the generics that your clients manufacture at the hearing?

MR. BARTLE: Because this case isn't about generics.

MR. DUCK: Well, it is, but you're saying that's your view, is that right?

MR. BARTLE: Well, you didn't allege it against our clients, number one; and number two, there's no fraudulent misrepresentation alleged as to Teva.

MR. DUCK: Okay. Disagree, but we'll agree to disagree.

MR. PATE: Harvey, before we jump off, I know -- I assume you guys are going to be on at 11:00 to talk about the depositions?

MR. BARTLE: Some of us will.

MR. PATE: Okay. So before we jump off to -- to get on that call, you had mentioned at the hearing that you would send a list of search terms. Do you have that list or --

MR. BARTLE: Yeah, I do. We'll get that to you.

MR. PATE: Okay. All right. Thank you.

MR. DUCK: One last thing. Hey, have you all heard from Paul LaFata about the HIPAA protective order?

MR. BARTLE: I think that should be done soon.

MR. DUCK: Okay. Good. Because he and I had a conversation, and the concern that he had, it was just a misunderstanding, and I think we got it resolved. So he said that he was going to try to work with the other Defendants, including you all, on getting us an answer about whether it's ready to go. So I didn't know if that was you all or someone else

in your group.

MR. BARTLE: No, I think that should be coming to you shortly.

MR. DUCK: Fantastic. Thanks, Harvey.

MR. PATE: All right. Thank you, all.

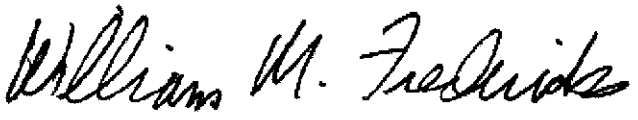
(Conference concluded.)

STATE OF TEXAS)
COUNTY OF TRAVIS)

I, WILLIAM M. FREDERICKS, CSR No. 2392, do hereby certify that there came before me on April 4, 2018, at 10:05 o'clock a.m., in the offices of Nix Patterson & Roach, 3600 North Capital of Texas Highway, Suite 350B, Austin, Texas, the foregoing proceedings, said proceedings transcribed by computer-assisted transcription by me or under my supervision, and that the transcript is a true record of the proceedings had.

I further certify that I am neither attorney nor counsel for, nor related to or employed by, any of the parties to the action in which these proceedings were had and, further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, or financially interested in the action.

IN WITNESS WHEREOF I have hereunto set my hand and affixed my seal on this 6th day of April 2018.



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IN THE DISTRICT COURT OF CLEVELAND COUNTY

STATE OF OKLAHOMA

STATE OF OKLAHOMA, ex rel., MIKE HUNTER ATTORNEY GENERAL OF OKLAHOMA, Plaintiff, vs. (1) PURDUE PHARMA L.P.; (2) PURDUE PHARMA, INC.; (3) THE PURDUE FREDERICK COMPANY; (4) TEVA PHARMACEUTICALS USA, INC; (5) CEPHALON, INC.; (6) JOHNSON & JOHNSON; (7) JANSSEN PHARMACEUTICALS, INC.; (8) ORTHO-McNEIL-JANSSEN PHARMACEUTICALS, INC., n/k/a JANSSEN PHARMACEUTICALS; (9) JANSSEN PHARMACEUTICA, INC. n/k/a JANSSEN PHARMACEUTICALS, INC.; (10) ALLERGAN, PLC, f/k/a ACTAVIS PLC, f/k/a ACTAVIS, INC., f/k/a WATSON PHARMACEUTICALS, INC.; (11) WATSON LABORATORIES, INC.; (12) ACTAVIS LLC; AND (13) ACTAVIS PHARMA, INC., f/k/a WATSON PHARMA, INC., Defendants.	Case No. CJ-2017-816

TRANSCRIPT OF PROCEEDINGS
HAD ON APRIL 19, 2018
AT THE CLEVELAND COUNTY COURTHOUSE
BEFORE THE HONORABLE WILLIAM C. HETHERINGTON, JR.
RETIRED ACTIVE JUDGE AND SPECIAL DISCOVERY MASTER
AND THE HONORABLE THAD BALKMAN
DISTRICT JUDGE

REPORTED BY: ANGELA THAGARD, CSR, RPR

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defendant or the burden on the defendants to produce them.

Finally, your Honor, I would like to respond to the State's follow-up argument that was made late Friday in a letter prior to the Easter holiday, that generics -- this generics argument, that argument is misleading. And it doesn't support expanding the scope of discovery beyond 2007 or to conduct not connected to Oklahoma.

As you see in the briefs, Oklahoma law is clear that discovery is necessarily limited to the actual claims and defenses that have been asserted in this specific lawsuit. While the State makes broad general allegations about the defendants manufacturing generics, the manufacturing of generics is not relevant to the actual claims they've pled.

As the State expressly pleads in the petition, argues in every brief in every hearing, and they argue it in page 4 in the brief they filed last night, the alleged basis for every one of the State's claims is fraudulent promotion and marketing of opioids.

For good reason, there's not one allegation in the petition about Teva or Cephalon promoting or marketing generics. Neither company has ever promoted or marketed generics. Cephalon has never even manufactured generics, much less promoted them.

While Teva manufactures generics, it's never marketed or promoted; thus generics simply aren't relevant to the State's

asserted claims and cannot justify expanding the scope of discovery beyond 2007 or to conduct not logically connected in any way to the state of Oklahoma.

So for those reasons, your Honor, Teva and Cephalon respectfully submit to the Court that discovery should be limited to conduct occurring from 2007 forward that is logically connected to Oklahoma. And that would include documents concern policies, practices, and procedures.

They're not limited on their face to Oklahoma to accommodate the State's allegation of this nationwide marketing campaign. That's all I have.

THE COURT: All right. Thank you.

MR. BRODY: I'll try to keep this to about 90 seconds, your Honor. When the State filed its motion to compel, on the second page of the motion to compel, it indicated that it's clear that there are certain discovery issues that are ripe for resolution related to all defendants and some that are specific to each defendant as set out below in its motion.

The issues that were raised with respect to Janssen and the areas of disagreement with respect to Janssen were very narrow. We touched on those at the last hearing. And in particular, as to Janssen's production, Janssen and the State had engaged in productive negotiations, reached agreements on the scope of discovery in response to various requests.

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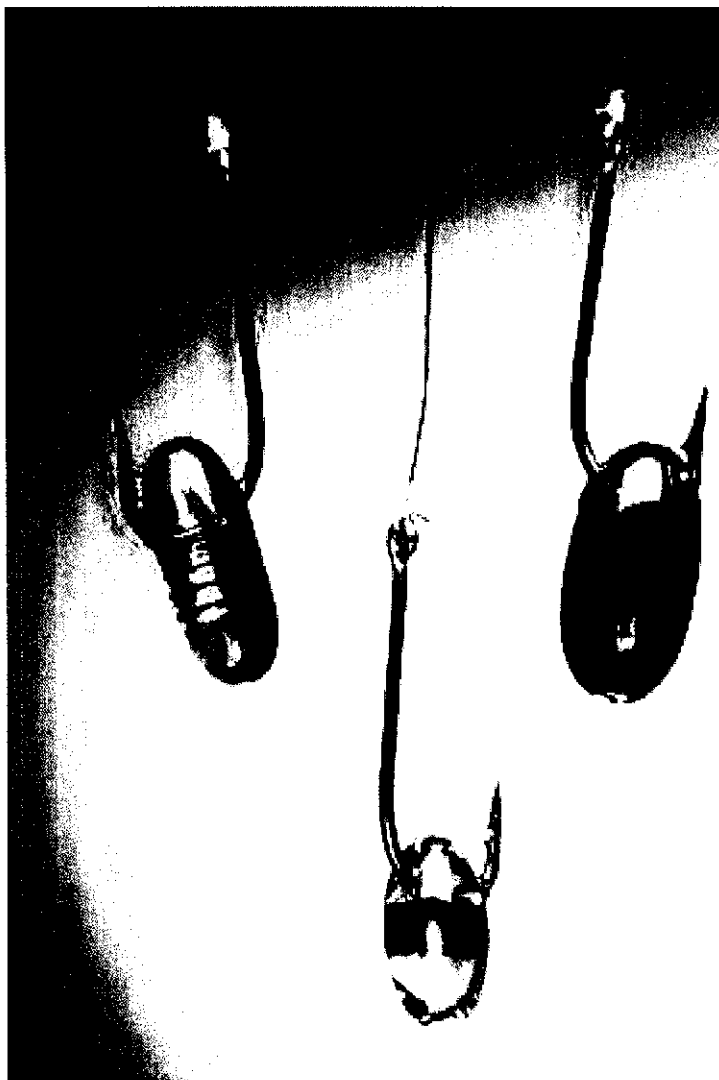

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Advances in Pain Management is supported by an educational grant from Cephalon.

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Publisher's Statement
 Advances in Pain Management (ISSN 1466-7401) is published four times a year. Subscriptions are available at the following rates: Europe Eur150; USA, Canada and all other territories US$200. Additional subscription information is available from the publisher.

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Design and Artwork: AS&K Skylight Creative Services

ISSN 1466-7401

Contents

EDITORIAL

Treatment of Pain with Opioids and the Risk of Opioid Dependence: the Search for a Balance

Ricardo Cruciani, MD, PhD

Beth Israel Medical Center, New York, NY, USA

The guiding paradigm for long-term opioid therapy has evolved significantly. Two decades ago, a cultural shift from pain opioid phobia to pain free seemed well on its way. At that time, evidence of undertreatment of pain was accumulating and the paradigm shift was motivated by the noble objective of providing help for suffering patients. Although evidence of long-term opioid effectiveness and safety was lacking, accumulated experience suggested that opioid therapy would provide enhanced comfort and improved function for a large numbers of patients with cancer or non-cancer pain [1]. A medical community that could grasp the straightforward pharmacotherapeutic principles and resist the unjustified drag of stigma and regulatory fear would have the opportunity to drive a large and sustained benefit to public health.

Although it was widely acknowledged that opioids are abusable drugs, there was no recognition of the risks linked to chemical dependency, including abuse, addiction, and diversion. Well-meaning pain specialists used data that were not relevant to chronic pain therapy and a risk–benefit analysis that prioritized redress of undertreatment above public health concerns related to addiction in order to promulgate reassuring messages that implied, essentially, that the management of abuse, addiction, and diversion was not a key issue in the practice of pain medicine.

The paradigm has shifted again. Pain specialists have seen the steady rise in national measures of prescription drug abuse and the devastation associated with endemic areas of high abuse. The fact that inadequately trained clinicians trying to do the right thing can cause real harm to individuals and to the community is now realized. The medical community overall has realized that regulators and law enforcement, charged with protecting the public health, will react negatively to rising abuse and may not temper this reaction with a careful analysis of the effect on pain treatment.

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These observations have supported a national policy of "balance", which highlights the need for policies that both protect medical use of long-term opioid therapy and concurrently reduce public harm associated with drug abuse and diversion. Addiction presents a significant societal burden, and there is now a growing problem of prescription drug abuse that has the potential to create a public health disaster. In order to combat this potential disaster, comprehensive education and a review of the evidence of prescription drug abuse and its relationship to pain management is essential for pain specialists so that they may learn how to derive the benefits of opioid therapy (pain control, functional gains), screen for addiction risk in individual patients, and employ a range of tailored management strategies to deliver opioid therapy in the safest way possible for each individual [2,3]. In cases of substance abuse, it is essential that clinicians know which therapy is the most suitable. Starting a patient on opioid therapy is not a "one way street". Reassessment must be done periodically and decisions made on continuation or change of strategies. An exit strategy should be considered if "red flags" are observed and alternatives to treatment be considered.

The identification of red flags can be facilitated by following the "4 As" rule. This is a useful mnemonic device for the relevant domains of outcome for pain management (the 4 As: analgesia, activities of daily living, adverse events, and aberrant drug-taking behaviors) [4,5]. The 4 As remind clinicians that a successful outcome in pain therapy encompasses more than the just the lowering of pain-intensity scores. The 4 As reflect a pain-relief therapy that makes a true difference in the patient's life, including stabilization or improvement of psychosocial functioning, manageable side effects (that do not compromise important areas of functioning), significant pain relief and negligible or absent aberrant behaviors. Nowhere is there a need for greater understanding and enhanced assessment ability than in the area of aberrant drug-related behaviors.

Safe and effective opioid therapy requires that clinicians both optimize pharmacological outcomes and undertake the assessment and management of risks associated with abuse, addiction, and diversion. However, when discussing their education, physicians, nurses, psychologists, and other care providers frequently report that their training included only little formal teaching about pain, addiction, and their interface [6]. In educating physicians regarding the pain/addiction interface, steps towards mastering the empirical and clinical domains are needed. For the clinical practice of pain management to make real progress, communication between these domains is essential.

Every patient who is treated with potentially abusable drugs should undergo proactive risk assessment, risk stratification, and an approach to treatment that provides monitoring commensurate with risk. No one regimen can be right in every case, but every case deserves assessment and thoughtful implementation of therapy. Risk assessment and risk management represent a new skill set for many clinicians. However, the strategies can be easily learned and practice will improve sensitivity. Tools to assess different elements of risk are now available and may eventually prove useful in practice, as well as in future research [7]. Clinicians should be encouraged to incorporate systematic assessment of risk, whether or not a validated tool is used. Assessment of the risks and benefits associated with opioid therapy, followed by a plan of action based on the findings is the key to safe and effective treatment.

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LEADING ARTICLE

Screening and Stratification Methods to Minimize Opioid Abuse in Cancer Patients

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A certain segment of patients who are prescribed opioids for pain will eventually abuse or become addicted to their medication. This article reviews universal precautions and screening devices germane to preventing abuse in patients treated using opioids, with a special emphasis on patients who have cancer pain. The available opioid-specific assessments, the need for patient risk stratification, and the importance of ongoing monitoring and periodic treatment adjustment to maximize outcomes will be discussed. Patient risk factors that can contribute to the risk of opioid addiction or abuse are also reviewed. *Adv Pain Manage* 2008;2(1):4–8.

Patients with cancer are often said to be at a low risk of abusing their pain medications. However, the rise of prescription opioid abuse has focused attention on the need for prevention in all exposed populations. The 2006 US National Survey on Drug Use and Health found that 5.2 million Americans aged ≥12 years misused prescription analgesics, an increase from 4.7 million in 2005 [1]. Furthermore, analgesics was the drug category with the greatest number of new initiates.

As the rate of mortality from cancer is reduced, the focus has moved from tacit approval of less oversight of cancer patients to ensuring such patients are not obliged to shoulder additional burdens, namely the illness of addiction or the problems of drug abuse. Screening patients to determine their risk of drug abuse prior to beginning opioid therapy is considered good practice. Even more vital is monitoring patients to ensure compliance, a process that was associated with a 50% reduction in opioid abuse in a study of 500 patients receiving controlled substances [2]. Many experts embrace universal precautions as applicable to all patients beginning opioid therapy to ensure at least minimal prevention of harm [3]. In addition to initial screening, these precautions include discussing and signing an opioid treatment agreement with the patient. The very notion of universal precautions suggests that what applies to non-cancer patients also applies to those with cancer.

Before beginning the following discussion, it is important to clarify the terminology used to describe opioid use and misuse. Table 1 gives an overview of common definitions that are used to describe opioid use and abuse, although these are subject to confusion even among physicians [4,5].

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Prevalence of opioid abuse and addiction

In terms of opiate addiction (leaving aside other substances, including alcohol), one study showed that 2–5% of chronic non-cancer pain patients manifested true addiction, marked by impaired control, compulsion, craving, and continued use despite harm [6]. That represents at least twice the rate of 1% found in the general population. Similar results were reported in a study showing that 4% of 801 adults receiving opioid therapy in primary care centers had an opioid use disorder – a prevalence four times that in the general population [7].

Cancer patients are usually presumed to be at a lower risk of opioid abuse than non-cancer patients. A recent literature review found "addiction" rates between 0% and 7.7% in cancer patients, but variations existed in the populations studied and criteria applied [8]. The greatest risk for patients with cancer pain is still that they will receive inadequate analgesia. However, a minority of patients who exhibit problems managing their opioid treatment, or who have a history of substance abuse, deserve attention to these risks as well as to pain relief.

Minimum steps to prevent opioid abuse

To achieve a workable clinical solution that addresses both pain control and proper use of medication, physicians preparing to treat patients with opioids should undertake the following [9]:

Table 1. Definitions associated with opioid use and abuse [4,5].

Misuse
The use of any medication by a person for whom it was not prescribed or for purposes other than those for which it was prescribed.

Abuse
A maladaptive pattern of substance use leading to clinically significant impairment or distress; intentional overuse in cases of celebration, anxiety, despair, self-medication, or ignorance.

Addiction
A primary, chronic neurobiological disease influenced by genetic, psychosocial, and environmental factors. Addiction is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.

Tolerance
A physiological state resulting from the regular use of an opioid in which increased doses are needed to maintain the same effects. In analgesic tolerance, increased opioid doses are needed to maintain pain relief.

Physical dependence
A physiological state characterized by abstinence syndrome (withdrawal) if an opioid is stopped or decreased abruptly or an opioid antagonist is administered. Dependence is an expected result of opioid therapy and does not, by itself, equal addiction.

- Familiarize themselves with the individual risk factors for opioid abuse.
- Screen new patients during their initial clinic visits to evaluate, diagnose, and possibly predict abuse or addiction in patients.
- Set the level of monitoring appropriate to the degree of risk demonstrated by the patient.
- Watch for and document any aberrant, drug-related behaviors that may be associated with abuse or addiction. Adjust monitoring measures accordingly.
- Reassess the patient at frequent intervals. Every visit should include some degree of reassessment.
- Never make judgments prior to an appropriate assessment. Do not assume that a high-risk patient will always abuse opioids or that a low-risk patient never will.

These measures also help to combat diversion of opioids to non-medical channels. Good monitoring will facilitate proper prescribing so that the patient, whether suffering from cancer or non-cancer pain, receives the correct amount of medication. Surpluses of medication in the home are at risk of theft by friends, relatives, or visitors who are looking to obtain opioids to abuse.

Risk factors for opioid abuse

Most tools used to assess individuals for the presence of or potential for opioid abuse are based on risk factors assembled from the literature or expert opinion. Risk factors include, but are not limited to, the following [6,10–12]:

- Personal history of substance abuse.
- Family history of substance abuse.
- Young age.
- History of preadolescent sexual abuse.
- Mental disease.
- Social patterns of drug use.
- Psychological stress.
- Lack of a 12-step program.
- Poly-substance abuse.
- Poor social support.
- Cigarette dependency.
- History of repeated drug/alcohol rehabilitation.

Opioid-specific screening tools

Several opioid-specific screening tools are available for risk assessment in patients with chronic pain. Selection of the appropriate tool will be based on the time available, the treating clinician's own expertise or access to experts in the fields of pain and addiction, and many other aspects of the clinical situation. Although the assessments discussed in the following sections have some clinical and research support, none has yet been fully validated in a variety of settings and populations. Perhaps more important than the tool chosen is the commitment to consistently assess patients as part of routine practice. Pending further research, clinicians should assess patients using the best available combination of questions. The clinician should bear in mind that literacy or English-language deficits can impair a patient's comprehension, and should be prepared to answer questions or administer assessments verbally.

Prescription Drug Use Questionnaire

The Prescription Drug Use Questionnaire (PDUQ) is a 42-item interview with questions regarding the patient's pain condition, opioid use, social and family history, and psychiatric issues [13]. In a pilot study, non-addicted subjects scored 6–25, substance-abusing subjects 11–25, and substance-dependent subjects 15–28. All subjects scoring >15 later satisfied criteria for substance use disorders.

Three items from the PDUQ appeared to be especially accurate in identifying people with substance use disorders:

- Tendency to increase analgesic dose or frequency.
- Preference for a specific route of administration.
- Consideration of oneself as addicted.

A drawback is that with 42 questions, the PDUQ takes longer to administer than is practical in many clinical settings. A patient-administered version of the PDUQ is currently in development.

Table 2. The Opioid Risk Tool [6].

Item	Mark each box that applies	Item score if female	Item score if male
1. Family history of substance abuse			
Alcohol	[ ]	1	3
Illegal drugs	[ ]	2	3
Prescription drugs	[ ]	4	4
2. Personal history of substance abuse			
Alcohol	[ ]	3	3
Illegal drugs	[ ]	4	4
Prescription drugs	[ ]	5	5
3. Age (mark box if 16–45 years)	[ ]	1	1
4. History of preadolescent sexual abuse	[ ]	3	0
5. Psychological disease			
Attention deficit disorder, obsessive–compulsive disorder, bipolar, schizophrenia	[ ]	2	2
Depression	[ ]	1	1
Total	___	___	___

Total score risk category: Low risk: 0–3; Moderate risk: 4–7; High risk: ≥8

ORT

The Opioid Risk Tool (ORT) is a five-question, self-administered assessment that can be completed within 5 min and should be utilized on a patient's initial visit (Table 2) [6]. It assesses the subject for personal and family history of substance abuse, age, history of preadolescent sexual abuse, and for the presence of depression, attention deficit disorder, obsessive–compulsive disorder, bipolar disorder, and schizophrenia. In a pilot study of patients with chronic pain, the ORT accurately predicted which patients were at the highest and lowest risks of exhibiting aberrant, drug-related behaviors associated with abuse or addiction. Examples of these behaviors include using more opioids than prescribed, selling prescriptions, losing prescriptions or reporting them stolen, canceling clinic visits, and forging prescriptions.

SOAPP

The Screener and Opioid Assessment for Patients with Pain (SOAPP) measures the risk of aberrant drug-related behavior in opioid-treated patients with chronic pain, and has been tested as a five-, 14-, and 24-item questionnaire [14,15]. Most recently, a version including the 14 items found to be most predictive of aberrant drug behaviors has been validated and published [15]. The SOAPP categorizes patients as high- or low-risk for opioid abuse based on a cutoff score of ≥8. Although the five-item questionnaire is less sensitive and specific than longer versions, it may suffice for use in primary care settings when time is short. While the SOAPP is intended to predict which patients may exhibit drug-related aberrant behaviors in the future, the Current Opioid Misuse Measure (COMM) is designed to help clinicians identify current opioid patients who exhibit abuse behaviors [16]. Information on the SOAPP and the COMM is available from the www.painedu.org [17].

SISAP

The Screening Instrument for Substance Abuse Potential (SISAP) uses five questions about the patient's age and use of alcohol, cannabis, and cigarettes to identify individuals at risk of abusing opioids, but does not address risks related to psychiatric comorbidities [18]. The SISAP has not been prospectively validated in a chronic pain population. However, tested against a large database of nearly 5000 telephone survey responses in a Canadian epidemiological survey of alcohol and drug use, the SISAP correctly classified 91% of substance abusers and 78% of non-abusers. This tool may be useful in a busy clinical practice when the presenting patient has a known history of substance abuse.

DIRE score

DIRE (Diagnosis, Intractability, Risk, Efficacy) score is a seven-item, physician-administered tool that is designed to predict which chronic non-cancer pain patients will achieve effective analgesia and be compliant with long-term opioid therapy [19]. A score of ≤13 suggests an unsuitable candidate, and a score of ≥14 suggests a good candidate.

Table 3. Matching monitoring to the patient's risk of drug abuse*.

Low risk (routine)	Moderate risk	High risk
Pain assessment	Biweekly visits	Weekly visits
Substance abuse assessment	Biweekly prescriptions	Weekly prescriptions (on attendance)
Informed consent	Regular prescription database check	Quarterly prescription database check
Signed treatment agreement	Verification via family members/friends	Friend/family member controls medication
Regular follow-up visits, prescriptions	Random UDT	UDT: scheduled and random
Initial prescription database check	Question comorbid disease	Consider blood screens
Medical reports	Consider psychiatric/pain specialist evaluation	Psychiatrist/addiction-specialist evaluation
Initial UDT	Consider medication counts	Consider pain specialist evaluation
No specialist consultation required	Consider limiting rapid-onset analgesics	Limit rapid-onset analgesics
Medication type, unrestricted		Consider limiting short-acting opioids
Document 4 As (analgesia, activities, adverse events, and aberrant drug taking)		
Document patient–physician interactions		

*Monitoring measures should be modified based on upon the condition of the patient. Patients who are very ill or are declining rapidly will not need the same level of assessment and monitoring as patients with a longer life expectancy. UDT: urine drug testing. Redrawn with permission from [9]

Facilitating honest self-reporting

It is important to build trust and rapport during the assessment process to encourage and facilitate the honest sharing of information. The validity of the information provided is enhanced when:

- Confidentiality is observed.
- Patients do not fear negative consequences from disclosing information.
- The information disclosed has a likelihood of subsequent verification.
- The clinician is non-judgmental and matter-of-fact.
- The clinician treats substance use questions as an important, routine component of the medical history, no different than data on diet, exercise, and smoking.

Experts on substance abuse counseling declare confrontational approaches to be less effective than empathic ones. A caring, non-judgmental clinician, who is nonetheless willing to set and implement treatment boundaries, provides an indispensable component of good medical care.

Monitoring the patient

The purpose behind stratifying patients into risk categories is not to deny high-risk patients pain treatment but to ensure that all patients receive appropriate monitoring and clinical vigilance. Table 3 contains suggested monitoring measures geared to different levels of abuse risk [9]. All patients should receive at least the minimum level of monitoring, with these measures intensifying as the risk level rises.

Bearing in mind the fact that the cancer patient's needs may be mainly palliative, it is not advisable to enact the same type of stringent monitoring measures when treating a cancer patient with a short life expectancy as when treating a non-cancer patient. The focus of monitoring terminal cancer patients should be on whether substance abuse is interfering with their treatment or quality of life.

Clinicians should monitor patient response to opioid treatment based on "the 4 As" – analgesia, activities, adverse events, and aberrant drug taking [20]. Every clinic visit should trigger an entry in the patient's chart covering each of these four areas; the Pain Assessment and Documentation Tool is helpful in this regard [21].

Patients may move from one risk category to another, particularly in response to stressors such as unrelieved pain, worsening disease progression, struggles with insurance coverage, and changes in financial status or social support systems. Co-treatment of comorbidities such as mental or anxiety disorders contributes to better outcomes. Patients with histories of substance abuse present a specific clinical challenge but can be successfully treated with opioids given the appropriate monitoring measures.

Special considerations for cancer patients

In patients with cancer who also have histories of substance abuse, care must be taken that active addiction is not re-triggered. Any active substance use disorder threatens compliance with medical direction, resulting in compromised cancer treatment. The risks of non-compliance include [22]:

- Shortened life expectancy due to the progression of addictive disease.
- Altered cancer prognosis due to interference with pain therapy.
- Predisposition to other serious morbidity.

- Damage to the patient's relationship with the treatment team.

Therefore, assessing patients for the risk of abuse and monitoring their response to opioid therapy are top clinical priorities. Steps to decrease substance abuse should go hand-in-hand with pain therapy.

It is also important to consider the stage of cancer when deciding what type of initial evaluation and monitoring to use. Today, many cancer patients live longer than sufferers did in the past, and so are at greater risk of substance abuse. These patients may derive benefits from assessment and monitoring in the same way that non-cancer patients do. However, a surprise diagnosis and a rapid progression of the disease should change the priorities. The focus should be less on the potential for abuse or addiction and more on meeting the patient's emotional and spiritual needs. If such a patient is at low risk for substance abuse, there is little to be gained by an insistence of intense monitoring. Even if the patient is at high risk and has a short time to live, it is more practical and more humane to ensure pain is adequately treated rather than to inflate concerns that the patient may use an opioid for an unintended purpose.

In former times, medical professionals went so far as to recommend withholding opioids from cancer patients in order to spare them the indignity of addiction. It makes far more sense to preserve the dignity of dying patients by not encumbering them with assessments that serve no purpose.

Conclusion

Patients, including cancer patients, have varying risks for drug abuse. Some risk factors are stable (e.g. a history of substance abuse) and others change over time (e.g. the stress that occurs with a deteriorating physical condition). Assessing patients for the risk of opioid abuse prior to beginning pain therapy provides a framework for appropriate monitoring and choice of therapy. Higher-risk patients will require more clinical vigilance but have the same rights to adequate analgesia as low- or moderate-risk patients.

Acknowledgment

Technical writing and manuscript review provided by Beth Dove of Lifetree Clinical Research and Pain Clinic, Salt Lake City, UT, USA.

Disclosure

Dr Webster has received research support and/or consultancy fees from Abbott, Advanced Bionic, Alpharma Pharmaceuticals, LLC, Ameritox, Arrya, AstraZeneca, Boehringer Ingelheim, Cephalon, CoMentis, Covidien, Durect, Elan, Elite, Forest, GlaxoSmithKline, Jazz, King Pharmaceutical, Medtronic, Merck, Nektar, Nervo, NeurogesX , Orthocon, Pain Therapeutics, Inc., Predix, Purdue, QRx Pharma, Respironics, Takeda, Torreypines, Wyeth, and Zars.

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LEADING ARTICLE

Appropriate Prescribing of Opioids and Associated Risk Minimization

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Chronic pain represents a significant health challenge and burden to our society. Often a controversial practice, pain management physicians must always be cognizant of issues of aberrant behaviors, abuse, and diversion while also providing high quality care to genuine patients who might benefit from therapy. A literature review of physician concerns about opioid prescribing for patients with chronic nonmalignant pain is provided, along with discussion of types of aberrant drug-taking behaviors, and tools to help physicians predict risk for problems with opioid management. A variety of self-administered and physician-administered tools differing in their psychometrics and intended uses have been developed, but not all have been validated for use in chronic pain patients seen in a clinical practice setting. Some tools assess abuse potential in patients being considered for opioid therapy, whereas others screen for the presence of substance abuse. By recognizing the psychometrics of each tool, clinicians can select the ones most appropriate for their patient population and screening needs. *Adv Pain Manage* 2008;2(1):9–16.

Chronic pain, currently experienced by approximately 75 million Americans, is becoming one the biggest public health problems in the US [1]. In the American Productivity Audit of >28 000 US workers, it was found that lost productive time resulting from pain conditions costs employers US$61.2 billion each year [2]. As the population ages, the societal and patient burden will undoubtedly increase. In a telephone survey carried out by USA Today, ABC News, and Stanford Medical Center on a random sample of American adults, results showed that although 63% reported to have sought medical help for pain, <50% believe that they have "a lot" of control over their pain, and fewer than one-third relied on complete or a "great deal" of pain relief [3]. Chronic pain affects physical, psychological, and social wellbeing, and patients with this disorder frequently experience sleep disturbance, depression, and anxiety [4].

Several surveys evaluating the adequacy of chronic pain treatment have reported a failure of the current system [5]. Patients are not often asked about pain and are frequently afraid to report any pain suffered; consequently, treatment options are not discussed or offered. Despite tremendous advances in the knowledge of pain pathophysiology, the understanding of treatments, and the development of multidisciplinary approaches to pain management, pain care is still grossly inadequate. Although there has been an explosion in pain research, new pharmaceuticals, the recognition of complementary and alternative therapies, interventional techniques and surgery, professional pain societies, and care providers who are board-certified in pain management, the undertreatment of pain is still considered to be pandemic. Primary care providers, often the first clinicians to see pain patients, are generally not prepared to manage the pain [6]. This is particularly true when primary care providers are faced with prescribing opioids as part of a patient treatment plan.

Just as the goal of diabetes therapy is not simply to lower blood sugar levels, proper pain management comprises more than just reducing pain levels from 10 to 0 on the typical Numeric Rating Scale for pain. The ultimate goal is to enable people with pain to live full and rewarding lives in the face of chronic illness and this is often best achieved through an integrative treatment plan that includes opioid therapy.

Chronic pain management and opioid prescribing: old and new thoughts

Care providers are concerned about finding the right balance between effective pain management and reducing a patient's risk of opioid addiction. Benefits of opioid therapy for nonmalignant pain were apparently seen as a result of educational efforts in the 1980s and 1990s. One pertinent

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example of this was the oft-cited Porter and Jick study [7], which was actually a letter to the editor detailing the relatively rare experience of addiction when looking at nearly 12 000 patients treated with opioids for acute pain episodes. Obviously, the idea that this experience was indicative of chronic pain patients was a significant leap. This, plus relevant clinical experiences of care providers who treat cancer and HIV/AIDS, led to the notion that opioids were safe and effective medications for the treatment of pain syndromes. Commonly articulated myths required new thought processes, as detailed in Table 1.

In the late 1990s, it became clear that treating pain with opioids for long periods of time often led to patient behaviors that were difficult to interpret. The existing model was to treat all chronic pain patients like terminal cancer patients. In clinical practice, it is well recognized that an 82-year-old patient with pancreatic cancer and a life expectancy of 3 months is different than a 35-year-old unemployed, injured worker with a history of substance abuse. In a 2005 study by the present authors in which opioid therapy in non-cancer pain was assessed, 45% of chronic pain patients showed behaviors suggestive of a lack of control over the use of opioids including early refills, dose escalation, and lost medication [8]. Without expertise and knowledge of opioid prescribing, misunderstandings between care providers and patients may occur, potentially leading to patients being accused of drug abuse when their aberrant behaviors were not followed closely enough in order to determine the cause(s) of the behavior. At that time, a new set of principles began to emerge for those studying and treating chronic pain patients, as summarized in the Table 2.

Guidelines for proper prescribing

Despite multiple guidelines and practice recommendations for the treatment of other chronic medical conditions, including diabetes, hypertension, and congestive heart failure, there are few such recommendations for the treatment of chronic pain. Medical boards recommend safe prescribing as detailed below, but do not suggest who should receive this class of medication. A consensus statement from the American Academy of Pain Medicine, American Pain Society, and the American Society of Addiction Medicine concerning the rights and responsibilities of healthcare professionals acknowledged the usefulness of opioid therapy as part of a pain management program and recommended that clinicians who prescribe opioids for the treatment of pain *"should use clear and reasonable medical judgment to establish that a pain state exists and to determine whether opioids are an indicated component of treatment"* [9]. Clinicians are implored to listen to the pain complaints of patients and to treat pain aggressively so as to increase the comfort and function of the individual.

Most pain specialists have prescribed opioids for long periods of time with success demonstrated by an improvement in function. However, all therapies have risks that must be managed, including adverse effects, the intentional or unintentional misuse of opioid therapeutics, and abuse. When considering opioid therapy, some patients, such as those with cognitive impairment, might be at increased risk of reduced psychomotor performance. Furthermore, those with a prior history of substance abuse might be at an increased risk for opioid abuse, misuse, and diversion. An appropriate treatment program would address the recommendations to prescribe opioids for chronic pain patients while acknowledging the risks, including aberrant behavior or abuse.

Reluctance to prescribe

As awareness of the undertreatment of pain has increased, the prescribing of analgesics has also increased. The emergence of cyclooxygenase-2 (COX-2) inhibitors stimulated a growth in the nonsteroidal class of drugs, until the cardiovascular effects became known [10]. Every class of analgesia, except COX-2 inhibitors, propoxyphene, and codeine, have had substantial increases in prescribing during the last 3 years, with hydrocodone compounds being the most widely prescribed medication in the US [11]. As there is now a wider availability of opioids, subsequently, there is also a greater degree of concern about public abuse. In the period 2002–2005 there were 190 million prescriptions for opioids in the US resulting in 9.4 billion doses [12]. In 2005, for the first time, opioids displaced marijuana to become the new illicit drug of choice, according to the National Survey on Drug Use and Health for that year [13]. The following year, the survey showed a minimum of 430 million abused doses [14]. More than 50% of the abused doses were obtained from friends or relatives of the abusers. At the same time, recent articles in prestigious journals have discouraged the use of opioids in chronic pain treatment, citing not only high risk but also lack of efficacy [15,16]. This negative trend is reconciled, at least somewhat, by recent work showing that opioids do have efficacy for subsets of patients who can remain on them long term and have very little risk for addiction [17].

Safe prescribing and the law

With regards to prescribing opioids, many clinicians find themselves in a difficult position; opioids are effective in reducing pain, but prescribing this class of drugs is more difficult than for other medications [17]. Unlike any other medication class, opioid prescribing requires documentation of informed consent or a treatment agreement.

The US Federation of State Medical Boards' 2004 *Model Policy for the Use of Controlled Substances for the Treatment of Pain* is widely used to develop Intractable Pain

Table 1. Commonly used approaches in the management of opioid side effects.

Myth	New thought
The mere exposure to an opioid leads to addiction	Patients function well on opioids and rarely show addictive behavior
Side effects limit opioid use	Most of the side effects are minimal or lessen with time. Many patients become tolerant to the majority of the side effects, but not to the analgesia
Opioids should be only used to treat severe pain	Treating pain early and aggressively leads to better quality of life, more function, and less chance of long lasting pain [44]
Chronic pain may be annoying, but it is not serious. Many people live with mild to moderate pain and are doing well	Quality of life can be significantly impacted by even mild chronic pain. The immune system is affected by pain and death rates increase with chronic pain, potentially including higher levels of suicide [45]

Table 2. Old thoughts and emerging principles for initiating opioid therapy.

Old thought	New thought
All patients deserve a trial of opioids	In some patients, opioids might present too many risks unless prescribed in a very controlled setting [46]
High pain levels require strong opioids	Pain levels alone do not dictate treatment. Treatment is a complex decision taking into account many factors, not just a pain score. The patient's pain history, social setting, and past history of substance abuse are at least as important as a pain score
Even addicts can be successfully managed on chronic opioid therapy	Practice management issues can overwhelm a care provider who is inexperienced with opioid therapy. Without experience and adequate support staff, addicts should not be managed with long-term opioid therapy. However, that is not to say that these patients cannot be treated. Some patients with pain are best managed in a primary care setting, some in a primary care setting with support from specialists, and some by a specialist with specific skills in an area of need, for example, a pain specialist, addiction specialist, or psychiatrist [46]

Acts, which promote appropriate pain management with an emphasis on the use of opioids [18]. By following these guidelines, practitioners can minimize suspicion and possibly avoid prosecution when prescribing this class of medication. At March 2007, a total of 29 states had adopted the *Model Policy* in whole or in part. In the last year, four additional states adopted medical board regulatory policies based on the *Model Policy* [19].

State policies aim to bring about the prevention of drug abuse, regulate professional practice, and improve patient care. These can, in turn, enhance or interfere with pain management [19]. Medical board guidelines, which do not have the force of law, outline simple steps needed for safe prescribing, but these same guidelines can sometimes be brought into a court of law and used against care providers when each step is not recorded. Most care providers discuss possible side effects with patients when starting them on new medications, yet when prescribing opioids, this discussion must be documented.

Ironically, the state medical boards who attempt to improve pain management are the same bodies that investigate care providers when overprescribing is questioned. The puzzle remains, what is overprescribing? How much is "too much" and what will trigger the board investigation? How "little" will result in patients and families of patients taking legal action against clinicians for not appropriately treating pain, part of which might include prescribing opioids? Such actions are just the beginning of the legal battle that has contributed to the fears among prescribers when considering opioid treatment. As a result, many physicians are now following ongoing monitoring protocols and using patient assessment tools to address the possibility of aberrant behavior and abuse by patients who are prescribed opioids.

The "4 As" for ongoing monitoring

Based on extensive clinical experience, the four domains hailed to be the most relevant for ongoing monitoring of chronic pain patients taking opioids are pain relief, side effects, physical and psychosocial functioning, and the occurrence of any potentially aberrant (or nonadherent) drug-related behaviors [20,21]. These domains have been

summarized as the "4 As" (analgesia, activities of daily living, adverse side effects, and aberrant drug-taking behaviors) [20]. The monitoring of these outcomes over time should affect therapeutic decisions and provide a framework for documentation of the clinical use of opioids.

In a previous study by the present authors and colleagues, the relationship between aberrant drug-taking behaviors and pain outcomes during long-term treatment with opioids for nonmalignant pain was examined in 388 patients from 27 pain clinics around the US [21]. The main focus of the study was on providing the nature, frequency, and predictive value of drug-taking behaviors in pain management. This effort could ultimately assist clinicians in the assessment and management of these behaviors, whether they resulted from the undertreatment of pain or from a substance use disorder.

The study also focused on the creation of a user-friendly checklist that clinicians could employ to examine the 4 As [21]. The checklist, developed by experts in pain and addiction medicine, was distributed to participating clinicians throughout the US, who evaluated patients who had been receiving opioid therapy for at least a period of 3 months using a structured interview approach and clinical observations.

Cross-sectional results in this study suggested that the majority of patients with chronic pain achieved relatively positive outcomes in all four relevant domains with opioid therapy. Analgesia was modest but meaningful, functionality generally stabilized or improved, and side effects were tolerable. Potentially aberrant behaviors were common (44.6% of the sample engaged in at least one aberrant behavior), but were only viewed as an indicator of a problem (i.e. addiction or diversion) in approximately 10% of cases. Thus, there is a clear need to document and assess the intricacies of aberrant drug-taking behavior in chronic pain patients.

Frequency of aberrant behavior

Passik and colleagues aimed to describe the frequency and types of aberrant behaviors in the above-mentioned study [21]. The study consisted of a cross-sectional look at aberrant behaviors noted over a 6-month period. Patients had a wide variety of pain complaints and were receiving a wide variety of opioids and medication combinations. Over the course of the study, 55% of the patients demonstrated no aberrant behavior, while the remaining 45% had at least two behaviors noted. Very few care providers would argue that all 45% of those patients are potentially addicted, and most agree that a myriad of causes can lead to noncompliance. However, only 6–10% of patients displayed evidence of five or more behaviors, numbers that are actually indicative of the prevalence of addiction in the population at large. These data highlight the fact that mere exposure to opioids does not cause aberrant behavior in everyone; particular patients possess vulnerabilities that will cause them to have difficulties in controlling their use of opioids when treated for chronic pain. Three or more behaviors in a 6-month period separates out approximately 20% of patients who will require more strict management as outlined below. However, "one strike and you're out" policies are not justified by these data.

In a follow-up study, Passik et al. also demonstrated that samples with differing baselines of addiction have predicted rates of aberrant behavior during opioid therapy [22]. The subjects in this study included 100 cancer patients and 75 patients who suffered from substance abuse disorders, which was their primary risk factor for HIV disease. Both groups were treated with opioids for pain relief. The AIDS patients were chosen to represent a sample population in which pain was caused by substance abuse; they had the same numbers of behaviors as the vulnerable subset of the chronic pain patients in the previous study [22]. Based on the base rate of addiction in the sample, the cancer patients showed fewer aberrant behaviors than the AIDS patients. The adequacy of analgesia provided to the AIDS patients was examined to determine whether opioids influenced aberrant behaviors (i.e. an attempt to empirically validate pseudoaddiction). It was found that this had no impact on their aberrant behavior.

The differential diagnosis of aberrant behavior

Empirical data is now available that may assist clinicians in their clinical decision-making and guide a response to observations of aberrant behavior. Clinicians will often see patients who display aberrant behavior, and in such cases they have to make a differential diagnosis – addiction or pseudoaddiction. Recent studies have shed some light on how to make this differential diagnosis. Passik et al. [22], Compton et al. [23,24], and Fleming et al. [25] all concluded that aberrant behaviors can predict addiction, whereas Wasan et al. [26] demonstrated that untreated, non-substance abuse-related psychiatric distress is the single biggest predictor of aberrant behaviors. Indeed, the concept of aberrant drug-taking behaviors and their impact on pain management continues to grow and gain acceptance [27–29]. Recommendations for making this differential diagnosis are summarized in Table 3.

Tools to assess the risk for patients taking opioids

As the acceptability of opioid therapy has expanded, there has been a growing realization that opioid use must be accompanied by risk stratification and management. The process begins with an assessment of addiction risk. Up until

Table 3. Differential diagnosis considerations for assessing aberrant drug-taking behaviors.

Differential diagnosis	Patient behavior
Addiction	Out-of-control behavior; compulsive, harmful drug use
Pseudoaddiction	Undertreated pain leads to desperate acting out; patients may turn to alcohol, street drugs, or doctor shopping; these behaviors subside once pain is adequately treated
Organic mental syndrome	Patients are often confused and have stereotyped drug-taking behavior
Personality disorder	Patients impulsive, have sense of entitlement, and may engage in chemical-coping behaviors
Chemical coping	Patients place excessive emphasis on the meaning of their medications and are overly drug focused
Depression, anxiety, and situational stressors	Patients marked by desire to self-medicate their mood disorder or current life stress
Criminal intent	Subset of criminals intent on diverting medications for profit

1 or 2 years ago, it was easy to bemoan the fact that there were only a few validated screening tools available for the prediction of aberrant behaviors in pain patients. In the past year, however, the need for more screening tools has been acknowledged and there has been a veritable increase in addiction-related screening tools, some formed and validated in pain patients. While a comprehensive listing has been undertaken elsewhere [30], the present authors have attempted to highlight several of the available instruments below.

Many screening tools require information on personal and family history of addiction as well as other history-related risk factors, such as preadolescent sexual abuse, age, and psychological disease, some particular to pain management and others that are simply risk factors for addiction in general. Selection and utilization of an assessment tool requires an understanding of tools that would be appropriate for the patient population that the assessment is aimed at. Whichever tool the clinician chooses, it is advised that the screening process be presented to the patient with the assurance that no answers will negatively influence effective pain management. Appropriate screening tools for assessing risk in pain patients are described below.

ORT

The Opioid Risk Tool (ORT) is a five-item tool with different weights for historical and psychiatric variables. Positive responses are assigned a weighted value rating based on the patient's gender, and the scores for all the possible items are added together in order to calculate the probability of opioid-related aberrant behavior. The ORT was evaluated by Webster and Webster in 185 new patients at a pain clinic [31]. Approximately 95% of patients with low-risk scores did not display aberrant behavior, while 90% of patients with high-risk scores did show aberrant behavior. These results demonstrate that the tool is valid and effective for predicting aberrant drug-related behaviors in a truthful sample of patients. ORT is considered the easiest and quickest way to assess a patient's risk, and is appropriate for many busy primary care physicians. However, if a patient is not forthcoming and truthful about his or her personal and family history of substance abuse, sexual abuse, and psychological disease, it can be ineffective.

SOAPP

The original Screener and Opioid Assessment for Patients with Pain (SOAPP) is a conceptually derived self-report questionnaire that can predict aberrant medication-related behaviors among chronic pain patients who are considered for long-term opioid therapy. Originally a 24-item tool, SOAPP was reduced to a 14-item version after Butler et al. tested each item's reliability [32,33]. Each item is measured on a five-point scale. A higher score indicates a greater risk of addiction. The revised version is perhaps the best tool psychometrically, and the most opaque. The low cut-off score (i.e. risk of addiction that is recognized even if patient under-reports aberrant behavior) makes this assessment tool less vulnerable to the possibility of deception. Therefore, SOAPP is preferable for high-risk populations that include patients who might be less than completely forthcoming about their medication use.

In a study by Butler et al., an empirically derived version of the original SOAPP (SOAPP-R) that addresses some limitations of the original was developed and validated [34]. This 24-item version is an improvement over the original because of enhanced psychometrics and risk potential-screening capabilities.

DIRE score

The Diagnosis, Intractability, Risk, Efficacy (DIRE) score was designed for the physician to predict which chronic nonmalignant pain patients will experience effective analgesia and be compliant with long-term opioid maintenance treatment. Diagnosis, intractability, efficacy, and four sub-categories of risk (psychological, chemical health, reliability, and social support) are rated from 1 to 3, with higher scores indicating a greater possibility of successful opioid therapy. Belgrade et al. tested the validity of the tool with an analysis of the DIRE score in 61 patients who had been treated with opioids for a median duration of 37.5 months at an outpatient pain management center [35]. The results indicated high sensitivity and specificity for predicting both compliance and efficacy. However, the study was retrospective and the patients had a variety of pain conditions. If validated with a prospective analysis of a more homogeneous pain patient population, the tool could be extremely useful for physicians who want to avoid possible deception by the patient. The tool is easy to use as it takes <2 min on average to complete; therefore, this tool is effective for the busy primary care physician.

COMM

A study by Butler et al. in 2007 was carried out with the aim of developing and validating the Current Opioid Misuse Measure (COMM) for those pain patients already on long-term opioid therapy [36]. A total of 227 chronic non-cancer pain patients were administered a 40-item alpha version of the COMM and the Prescription Drug Use Questionnaire, and were also asked to submit a urine sample for toxicology screening. Physicians were also asked to document the patients' aberrant behavior. A follow-up study among 86 patients with a version that contained 17 items of the alpha version that were found to adequately measure aberrant behavior indicated that the COMM was a promising and efficient way of assessing current aberrant behavior. Further study of this tool is needed, but it holds promise as a means of assessing current opioid misuse.

SISAP

The Screening Instrument for Substance Abuse Potential (SISAP) is a physician-administered, five-item measure that was never fully incorporated into major clinical practice. It contains a list of questions on associated behaviors or identifiers that demonstrate caution, including alcohol consumption, marijuana use, cigarette smoking, and age. Data from the National Alcohol and Drug Survey in Canada showed that SISAP was effective in identifying substance abusers; it correctly identified 91% of substance abusers and 77% of those who were nonabusers (n=4948) [37]. Although these results from such a large sample indicate the tool's potential, validation is needed in the form of prospective trials.

Urine screening and structured approaches to identifying opioid misuse

In addition to screening tools, new laboratory assessments and technologies for urine screening have been incorporated into pain clinics with the aim of yielding real-time answers for the clinician as to whether or not the patient is using illicit drugs and/or non-prescribed controlled substances. Physicians have a truth bias, in that they are trained to believe that people come to them wanting help, in good faith. Physicians need to continue to cultivate this view toward pain patients, but at the same time they must utilize prescription-monitoring programs and urine screens for verification of self-report, and in treatment planning. Katz et al. demonstrated that no matter how vigilant the clinician is at following aberrant behaviors, signs can be missed; one in five patients who appeared to be taking their medicines as prescribed by their expert clinicians were identified to be positive for an illicit drug upon urine screening [38].

Urine screening provides the advantages of a non-invasive, low-cost monitoring strategy that will detect most drugs for 1–3 days after exposure [39]. According to the Federation of State Medical Boards, urine screening can provide objective documentation of a patient's compliance with the treatment plan and opioid agreement, reduce the risk of an unrecognized opioid abuse problem, and justify the continuation of chronic opioid analgesic therapy in patients who adhere to the treatment plan and have acceptable urine screening outcomes [18]. Although this method is useful, urine drug screening results should be used as part of the overall clinical strategy, as the results are sometimes incorrect and both false positives and false negatives do occur on occasion. In addition, some compounds are not typically found in standard urine screens and more specific, expensive urine tests need to be ordered (or even blood or hair testing).

A recent study has tremendous implications for pain management as it provides the beginnings of empirical validation of management principles that have hither to been suggested merely on the basis of clinical experience. Wiedemer et al. reported on their experience of utilizing a specialized approach to responding to aberrant behavior in the Veterans Administration system in Philadelphia [40]. Patients in primary care pain management who exhibited aberrant behavior received a consultation with a nurse practitioner or a clinical pharmacist. The consultation yielded a "second-chance agreement". The second-chance agreement dictated the terms of remaining on opioid therapy, including frequent visits to the clinic, smaller

quantity of opioids per prescription, urine screens and/or pill counts, and addiction-related counseling as needed. Following the consultation, 38% of the patients self-discharged. However, 45% of the remaining patients were able to continue primary care pain management with this approach. This group of patients no longer exhibited aberrant behavior and were therefore considered compliant. This study represents the need for future efforts to further assess the efficacy of a structured, multifaceted approach to managing patients on long-term opioid therapy.

Cigarette smoking

It is important to recognize a behavior that appears to be an indicator of potential opioid misuse in many of the tools, that is, cigarette smoking. The connection between smoking and aberrant drug use is intriguing and deceptively complex. Not only is tobacco use highly prevalent among substance abusers [41], but people suffering from pain are also more likely to use tobacco [42]. The latter fact raises an important question: is this associated with nicotine's addictive properties or does it reflect the analgesic properties reported for nicotine?

Jamison was one of the first researchers to demonstrate how smoking is used as a means of trying to self-medicate pain. However, it is very important to recognize that the relationship might be more complicated than was originally believed [43]. This complex connection requires pain clinicians to answer an important question during their assessment: is smoking an indicator of pseudoaddiction, a proxy for other substance use, a co-occurring addiction in itself, or a form of self-medication?

Conclusion

Over the last 20 years, clinicians have struggled to reach a consensus on appropriate opioid prescribing. Although many of the commonly articulated myths about the risks and efficacy of opioids have been discounted by various members of the medical community, physicians still fear the risk of abuse or addiction as well as the potential legal consequences of their prescribing. The key challenge is balancing the benefits and risks of prescribing opioids in order to help patients live full and rewarding lives.

As a result of many studies designed to address this challenge in recent years, there are many excellent tools available to help practitioners determine how best to manage opioid prescribing in the face of potential drug abuse, addiction, and diversion. These tools include both patient- and physician-administered assessment measures used to determine the potential of drug abuse and aberrant behavior. In addition, medical boards have established guidelines to assist clinicians in developing effective strategies for encouraging compliance. By reviewing these tools and guidelines and adopting them into practice as appropriate, the physician will take a significant step in providing effective pain management for their pain patient, while minimizing risk.

Disclosures

The authors have no relevant financial relationships to disclose.

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LEADING ARTICLE

Prescription Drug Abuse and its Relationship to Pain Management

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The burden of chronic pain on healthcare systems is huge, with individuals who suffer from chronic pain often having multiple physical or psychological comorbidities. Opioid analgesics represent the cornerstone of chronic pain treatment; however, the potential for opioid dependence/abuse has generated much debate with regard to their widespread use. Historically, the non-medical use (abuse) of opioids has been documented since the 1700s, and detailed population investigations of prescription drug abuse have been undertaken since the 1970s. These, along with recent epidemiological analyses of prescription opioid abuse, and the phenomenon of prescription drug "diversion", are highlighted in this review. Large-scale studies performed by ourselves and others to assess prescription opioid usage, and the potential for iatrogenic abuse are also discussed. Such abuse appears to be less prevalent than perhaps is commonly stated, and the risk–benefit ratio for opioids in the treatment of chronic pain seems favorable. However, it should be emphasized that patients with extensive physical or psychological comorbidities are more prone to prescription drug abuse; thus, pain management specialists must use opioids carefully in such individuals. *Adv Pain Manage* 2008;2(1):17–29.

The health burden of chronic pain

Opioid analgesics are the cornerstone of chronic pain treatment; however, their potential for abuse is a subject of much debate. Individuals experiencing chronic pain often have numerous comorbid mental and physical illnesses, and, as such, represent a huge burden on a nation's healthcare system [1–4]. However, the latter conclusion is based on estimates and extrapolations from national surveys and, consequently, is an approximation at best. With respect to addressing the scope and magnitude of comorbidity, especially in a quantifiable sense, most studies conducted to date have used retrospective surveys [5–9], which collect self reports of illness, often in relatively small samples drawn from a few select treatment clinics. Accordingly, the results inadequately generalize to the total population, since those in treatment programs represent only a fraction of all patients receiving opioid pain medications. An additional limitation of existing studies is that they have largely relied on self-reported opioid drug use, and precise information on dosage and type of analgesic drug is typically limited.

To overcome these problems, we reasoned that a large medical insurance claims database would provide a more objective and quantifiable index of the use of opioid analgesics by those in chronic pain, their utilization of medical services, drugs prescribed and the prevalence of diagnosed physical and mental disorders. Hence, all medical and drug claims were extracted from a database provided by a Midwest subsidiary of a national managed care company for the state of Missouri, USA for the calendar year January 1–December 31, 2004. A 1-year period was used in order that measures of comorbidity would refer to concurrent disease rather than life-time prevalence, which could be determined in a longitudinal study. Three groups were defined:

- Acute opioid use – individuals who received one prescription for <10 days of supply of opioid analgesics in the calendar year (n=37 108, 9.1% of the insured population).
- Chronic opioid use – those who received ≥180 days of supply per year (n=3726, 0.92% of the total).
- Non-opioid group – individuals who filed one or more non-opioid insurance claims in the calendar year (n=337 336, 83% of the total).

The remaining individuals received opioids at levels that were intermediate between the defined acute and chronic groups and this group was excluded from the study. It should be noted that our definition of acute and chronic opioid use was arbitrary. However, our goal was to avoid "shades of grey" in the distinction between the two groups,

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Table 1. Health service utilization by chronic opioid, acute opioid, and non-opioid treatment groups in the state of Missouri, USA, in 2004.

Average number of service utilizations	Chronic opioid						Acute opioid						Non-opioid					
	All n=3726		Male n=1370 (37%)		Female n=2356 (63%)		All n=37 108		Male n=16 654 (45%)		Female n=20 454 (55%)		All n=337 366		Male n=164 596 (49%)		Female n=172 770 (51%)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Insurance claims	169.29	2.25	145.52	3.31	183.12	2.97	57.12	0.34	47.16	0.50	65.23	0.46	28.54	0.08	23.23	0.10	33.60	0.12
ICD9 diagnoses	20.66	0.23	17.70	0.35	22.38	0.29	11.61	0.04	9.74	0.06	13.06	0.06	7.79	0.01	6.64	0.01	8.76	0.02
Doctors seen*	9.81	0.12	8.57	0.19	10.52	0.15	6.34	0.02	5.46	0.03	7.02	0.03	3.39	0.01	2.68	0.01	4.06	0.01
Office visits	16.91	0.25	14.80	0.38	18.14	0.33	8.67	0.05	7.46	0.07	9.58	0.07	5.06	0.01	4.20	0.02	5.89	0.02
ED visits	0.62	0.03	0.53	0.04	0.67	0.04	0.31	0.00	0.32	0.01	0.30	0.00	0.11	0.00	0.10	0.00	0.11	0.00
Hospital days	1.66	0.09	1.42	0.14	1.80	0.12	0.56	0.02	0.45	0.03	0.64	0.02	0.22	0.01	0.18	0.01	0.26	0.02

ED: emergency department; ICD9: International Classification of Diseases 9; SE: standard error.

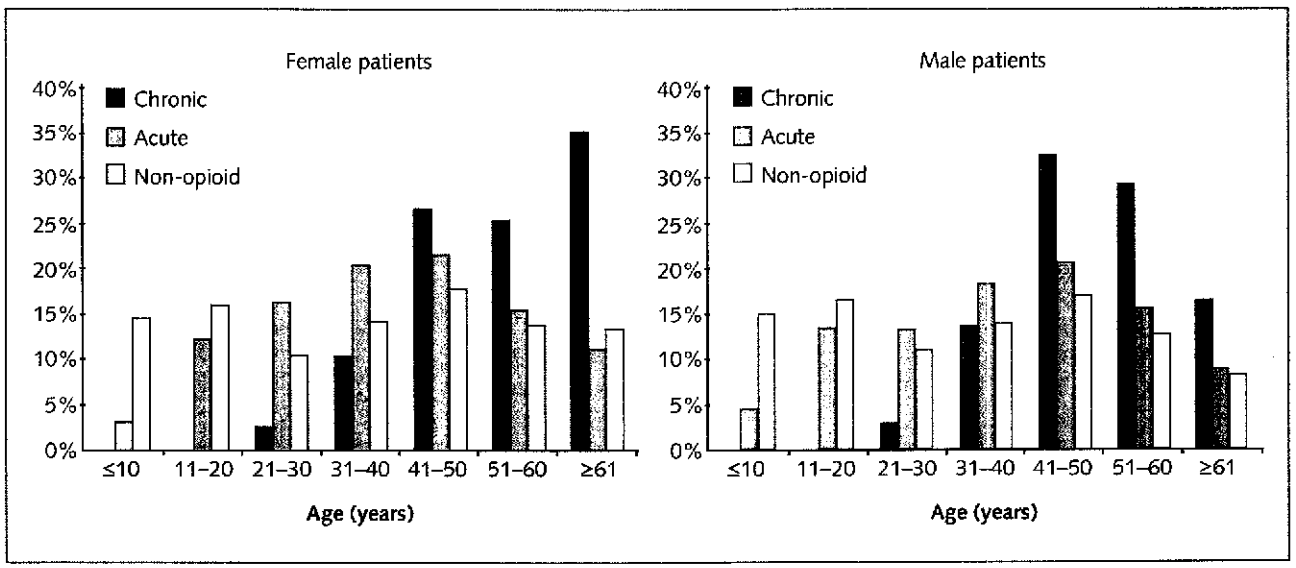
*Excluding radiologists and pathologists. SAS® multiple general linear models procedures were used to specify statistically significant differences (independent variables: groups and female). All estimated parameters were significant at $p<0.01$. *Post hoc* test of treatment group differences were all significant at $p<0.01$; *post hoc* tests of gender differences were all significant at $p<0.05$.

Table 2. Selected physical and mental health diagnoses in chronic opioid, acute opioid, and non-opioid treatment groups in the state of Missouri, USA, in 2004.

Diagnosis in 2004		Chronic opioid			Acute opioid			Non-opioid (%)		
		All	Male (37%)	Female (63%)	All	Male (45%)	Female (55%)	All	Male (49%)	Female (51%)
Pain	Muscle skeleton pain	75.6	74.6	76.1	36.0	35.2	36.7	16.9	15.0	18.6
	Abdominal pain	21.2	16.8	23.7	14.3	11.0	17.1	5.6	4.2	6.9
	Headache	18.8	13.7	21.8	8.0	5.1	10.3	3.9	2.6	5.1
Other physical health	Hypertension	43.1	40.5	44.6	18.5	18.8	18.3	13.7	13.1	14.2
	Endocrinological disorders	23.5	19.4	25.9	10.4	7.7	12.5	7.7	5.9	9.4
	Hyperlipidemia	21.4	24.3	19.7	11.2	12.7	10.1	8.7	9.4	8.0
	Reflux disorders	11.7	10.6	12.4	5.9	5.2	6.5	3.5	3.1	3.7
Mental health	Any mental health diagnosis	35.4	29.7	38.7	15.4	13.5	17.1	11.0	10.0	12.0
	Depression or mood disorders	22.0	16.4	25.3	8.0	5.6	9.9	5.0	3.5	6.5
	Anxiety disorders	11.0	9.2	12.0	4.2	3.14	5.0	2.7	2.0	3.4
Substance abuse	Opioid abuse/dependence	1.29	1.31	1.27	0.04	0.07	0.02	0.01	0.02	0.01
	Alcohol-related psychiatric disorder	1.23	2.26	0.64	0.52	0.79	0.3	0.28	0.41	0.15

SAS® multiple logistic regression model results (independent variables: groups and female). All estimated parameters were significant at $p<0.01$ except for "alcohol-related psychiatric disorder" between acute and non-opioid groups ($p=0.16$). *Post hoc* tests of treatment group differences were all significant at $p<0.01$; *post hoc* test showed gender differences were significant in the chronic group at $p<0.05$ except for muscle skeletal pain ($p=0.30$), opioid abuse/dependence ($p=0.91$), and reflux ($p=0.11$); *post hoc* test of gender differences were significant in both acute and non-opioid groups on all diagnoses ($p<0.05$).

Figure 1. Age distribution of chronic opioid, acute opioid, and non-opioid groups by gender.



by selecting two completely non-overlapping groups, which would presumably be more homogeneous.

The results shown in Tables 1 and 2 indicate that chronic pain patients – although comprising only 0.91% of the total insured population – were considerably more intensive consumers of all medical services than either the acute opioid or non-opioid groups. Collectively, these patients filed >5% of all medical insurance claims, received 45% of all opioids used in the state of Missouri, had many more non-pain-related diagnosed physical disorders, more psychiatric comorbidity, saw a significantly greater number of doctors, had more office and emergency department (ED) visits, and had a greater number of days in the hospital than the acute opioid use group or non-opioid group. As such, these numbers provide quantitative data to support prior extrapolations indicating that chronic pain patients have significant rates of comorbid physical and mental health-related problems and represent a disproportionately high percentage of those utilizing medical services [1–9]. As a result (and as stressed previously [10,11]), it seems clear that any comprehensive pain-management program should treat not only pain and the underlying physical disease state causing the pain, but also other comorbid physical and psychiatric conditions. Moreover, given the pharmacological complexity of managing pain with opioids (including breakthrough pain), the involvement of pain management specialists in the treatment plan for the majority of those in chronic pain seems appropriate for the provision of optimal treatment.

In a comprehensive analysis of the database described above, although females constituted 51% of the general population, the proportion of females increased with increasing intensity and persistence of pain: 55% of the acute opioid-use group and 63% of those in the chronic use group were female. Moreover, there was a clear age–gender interaction, as shown in Fig. 1. With increasing age, females became progressively more dominant, such that >80% of the chronic pain sample aged ≥61 years was female. Equally as important, when correcting for their numbers, females utilized all medical services to a much greater extent than males, and the difference increased as a function of the degree of opioid use (chronic > acute > none). Thus, females appear to have a considerably greater need for medical services than males, particularly those who have chronic pain requiring opioid analgesic therapy. Our studies provide quantifiable, population-based data that confirm and extend prior studies in which distinct gender differences were observed in terms of the incidence of pain, opioid treatment, and the comorbidity associated with chronic pain [12,13]. The reason for this large gender difference needs to be examined in greater detail in systematic psychosocial and biologically based studies (e.g. the role of sex steroids in the vulnerability to disease and the perception and treatment of pain). Until such studies are undertaken, it is important that pain management specialists consider gender as a critical variable in their treatment plans.

Our findings suggest that a diagnosis of opioid abuse is a rare phenomenon in the general non-opioid insured population, at <0.02% (Table 2). However, in the chronic opioid use group – while the rate was still low – it was more than 31- and 128-times greater in males and females, respectively, than in the non-opioid-using insured population. These data are significant from two perspectives:

firstly, females receiving chronic opioid therapy appear to be more prone to being diagnosed with an opioid abuse problem than males; secondly, the incidence of "iatrogenic" dependence in the chronic opioid group seems to be remarkably low.

With regard to the apparent increased vulnerability of females to the development of abuse while undergoing chronic opioid treatment, we are aware of no prior data to support this conclusion. However, there are data from *in vivo* studies in rats indicating that tolerance and physical dependence on opioids develop more rapidly in female than in male animals [14,15]. Our current data suggest that more systematic studies in humans need to be performed to examine this issue. The second supposition – regarding abuse generated as a function of chronic opioid administration – needs to be considered to some extent in the context of prior reports of iatrogenic dependence. Iatrogenic abuse and/or dependence, and the fear that it generates in physicians, has been the subject of intense, often heated, debate over the last several decades [16–19]. The relatively few systematic studies in this area have estimated the incidence of iatrogenic dependence of those maintained on chronic opioids at values from <1% up to as much as 30–40% [16–19]. Our data suggest that the actual number may be somewhat higher than the lower limit because of reluctance to report abuse by physicians [20–24] and the lack of involvement of psychiatrists and abuse experts in the treatment program, but it certainly does not reach the upper limit. Nonetheless, physicians should be aware of the possibility of opioid abuse when managing chronic pain patients taking opioids, particularly women. However, the fear that iatrogenic abuse is exceedingly common appears to be overstated.

Risk–benefit ratios of opioid analgesics

All drugs have adverse events associated with their therapeutic use. The dilemma for physicians and federal agencies is to decide how much risk is acceptable to offset the benefits of using a particular drug. In this decision-making process, it is important to stress that the rate at which an adverse event occurs as a function of legitimate therapeutic use of the drug is the most appropriate measure of a risk–benefit assessment, rather than the number of adverse events alone. This point is illustrated most clearly with nonsteroidal anti-inflammatory drugs (NSAIDs). In terms of number of adverse events alone, tens of thousands of people experience gastrointestinal bleeds attributable to NSAIDs, some of which are fatal (perhaps 15 000 deaths/year) or require hospitalization [25,26]. However, as these drugs are highly efficacious, they have a favorable risk–benefit ratio and continue to be widely used in clinical practice. Thus, if a drug control policy is based on simply the number of abuse cases and ignores the risk–benefit ratio, it would appear contrary to protecting public health.

The rate of an adverse event has traditionally been expressed as the number of adverse events divided by the number of people benefitting from the therapeutic use of the drug. Thus, if one reads a guide such as the Physician Desk Reference [27], rates of occurrence of adverse events are listed as the percentage of people who experience an adverse event while using the drugs therapeutically at the recommended doses. The problem with categorizing abuse as an adverse event, and hence, the calculation of a risk–benefit ratio, is that abuse is not generally associated with therapeutic use of opioid analgesics. Rather, diversion to an unintended population (e.g. recreational or street drug abusers) is the most frequent pattern of abuse. Thus, we believe that it is wrong to treat abuse as an adverse event that systematically develops as the opioids are used therapeutically. Indeed, there are very few data to suggest that abuse is a natural by-product of therapeutic use. Regrettably, regulatory agencies have frequently overlooked this point and have consistently designated abuse as the major risk associated with the therapeutic use of these drugs. It is necessary to change this emphasis on abuse for two reasons: firstly, such analyses place drugs with substance-abuse potential in an entirely different category to any other medically used class of drugs, which seems difficult to justify on any level; secondly, given the damaging effects of the decision to schedule drugs under the Controlled Substance Act on physicians' prescribing practices, very efficacious and valuable medications are used considerably less frequently than they should be. Taking all of these factors into consideration, we believe there is a more favorable risk–benefit ratio for opioids than for any other class of drugs. The enormous benefits of treating pain, which affects 47 million people worldwide, greatly outweigh the "risk" of abuse by non-patients.

The history of prescription drug abuse

The non-medical use of pharmaceutical opioids has been a longstanding problem in the US. There has been some speculation that the trend began early in the eighteenth century with the work of Thomas Dover, a student of British physician Thomas Sydenham [28]. Known as the "English Hippocrates" and the father of clinical medicine, Sydenham had been a strong advocate of the use of opium for the treatment of disease. Following the path of his mentor, Dover developed a form of medicinal opium known as "Dover's Powder", which contained one ounce each of opium, ipecac, and licorice, combined with salt-petre, tartar, and wine [29]. It was introduced in England in 1709, but quickly made its way to the American colonies and remained one of the most widely

used opium preparations for almost two centuries. The attraction of Dover's Powder was in the euphoric and anesthetic properties of opium, and its introduction apparently started a trend. Towards the latter part of the eighteenth century, patent medicines containing opium were readily available throughout urban and rural America, and by the closing years of the nineteenth century the abuse of these drugs had become widespread [28,30–32]. The abuse of opioids continued throughout the twentieth century. The first general population survey of drug abuse undertaken in the US, conducted in New York state in 1970, found the abuse of prescription opioids to be common [33]. Subsequent surveys, in addition to focused research studies, documented the continuing abuse of prescription opioids [34–38]. Moreover, from the 1970s to the 1990s, several prescription opioids cycled in and out of the American recreational drug scene – pentazocine ("Ts & blues") and propoxyphene in particular – while others, such as hydromorphone and hydrocodone, maintained a steady presence [37,39–42]. Towards the end of the 1990s, it had become clear from data gathered through the Drug Abuse Warning Network (DAWN), the National Institute on Drug Abuse Community Epidemiology Work Group, the Monitoring the Future surveys, and the National Household Survey on Drug Abuse (now referred to as the National Survey on Drug Use and Health [NSDUH]), that prescription opioid abuse was on the upswing [43].

The epidemiology of prescription drug abuse

The NSDUH found that the numbers of new, non-medical users of prescription opioids (primarily products containing codeine, hydrocodone, and oxycodone) increased from 600 000 in 1990 to >2.4 million in 2004, marking it as the drug category with the largest number of new users in 2004 [44]. In addition, reports from DAWN indicate that abuse-related ED visits involving narcotic analgesics increased by 153% between 1995 and 2002 [45], and during the same period, abuse-related ED visits involving benzodiazepines increased by 41% [46]. Similar increases are reflected in drug abuse treatment patients' admissions data [43]. As with illicit drugs, the precise number of prescription drug abusers would be difficult to estimate given the limitations of general population surveys. Nevertheless, some good indicators are available. The 2004 NSDUH, for example, found significant increases in the non-medical, lifetime use of prescription opioids among persons aged ≥12 years between 2002 and 2004 – from an estimated 29.6 million to 31.8 million users. Considerable increases have been observed among those aged 18–25 years in particular. In addition, data from the NSDUH indicate a continuing upward trend in the use of opioids during the past month. Among those aged 18–25 years, past-month, non-medical use of pain relievers increased from 4.1% in 2002 to 4.7% in 2004 [44].

The latest NSDUH figures also capture the increase popularity of particular types of prescription drugs. Specifically, between 2003 and 2004, statistically significant ($p<0.05$) increases occurred in the use of hydrocodone, aspirin–oxycodone, hydrocodone products, acetaminophen–oxycodone, and oxycodone products [44]. In addition, data from DAWN indicate that ED visits involving prescription drugs have been increasing. Specifically, in 2002, opioid pain relievers accounted for 10% of all drug mentions in ED visits, with hydrocodone and oxycodone making up the majority of cases. From 1994 to 2002, mentions of oxycodone increased by 450% (3393 to 22 397), while mentions of hydrocodone increased 170% (9686 to 25 197). The majority of the ED visits involved multiple drugs for both oxycodone (71%) and hydrocodone (78%), with the most frequently cited substances found in combination with these drugs being alcohol, benzodiazepines, other opioids, and cocaine.

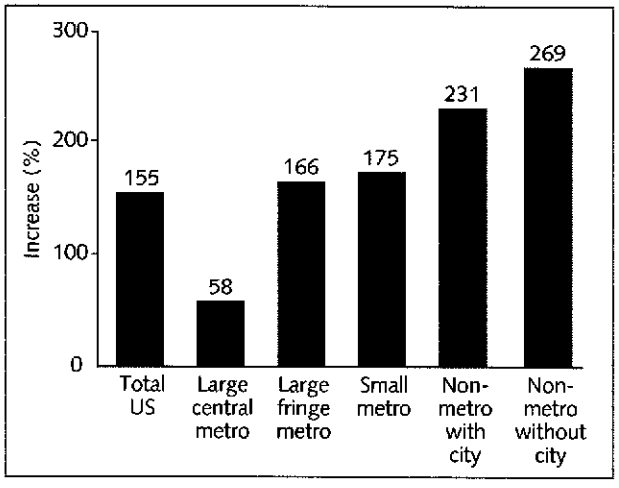
Drug abuse treatment admission data also indicate that prescription drug abusers represent a growing proportion of those enrolled for treatment. From 1993 to 2003, the admission rates for abuse/dependence on opioids other than heroin increased by 223% [47]. In 2003, there were 50 946 treatment admissions of primary non-heroin opioid abusers. Among these, almost 60% were poly-drug users with alcohol, marijuana, and tranquilizers among the most commonly reported secondary substances of abuse [47]. Moreover, data from 2003 indicate that >4% of the nearly 1.9 million documented treatment admissions mentioned a prescription drug as the primary complaint, with non-heroin opiates accounting for 2.8% of all admissions. Importantly, as illustrated in Fig. 2, treatment admission rates involving prescription opioids increased more in non-metropolitan and rural areas than in large urban areas.

The diversion of prescription opioids

Prescription drug diversion involves the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace [48], and the phenomenon has been a topic of widespread commentary since the latter part of the 1990s [43,49–53]. The Drug Enforcement Administration has estimated that prescription drug diversion is a US$25 billion-a-year industry [54], and that diversion can occur along all points in the drug delivery process, from the original manufacturing site to the wholesale distributor, the physician's office, the retail pharmacy, or the patient [55].

It is generally believed that the major mechanisms of diversion include the illegal sale and recycling of prescriptions by physicians and pharmacists; "doctor shopping" by individuals who visit numerous physicians to obtain multiple

Figure 2. Increase in rates of treatment admissions involving narcotic painkillers by urbanization from 1992 to 2002 [47].



prescriptions; theft, forgery, or alteration of prescriptions by patients; robberies and thefts from manufacturers, distributors, and pharmacies; and thefts of institutional drug supplies. Furthermore, there is growing evidence that diversion of significant amounts of prescription opioids occurs through residential burglaries [56–59] as well as cross-border smuggling at both retail and wholesale levels [60]. In addition, recent research by the National Association of Drug Diversion Investigators, and others in the prescription drug abuse field, has documented diversion through such other channels as "shorting" (undercounting) and pilferage by pharmacists and pharmacy employees; medicine cabinet thefts by cleaning and repair personnel in residential settings; theft of guests' medication by hotel housekeeping staff; and Medicare and Medicaid fraud by patients, pharmacies, and street dealers [48,60–62]. Moreover, it would appear that "pill-abusing" middle- and high-school students obtain their drugs through medicine cabinet thefts and medication trading. Finally, a number of observers consider the Internet to be a significant source for illegal purchases of prescription drugs [63,64], and there are likely to be many other sources.

Although national surveys and monitoring systems are documenting widespread abuse of prescription opioids, and numerous scientific papers over the years have discussed the problems associated with diversion [43,48,65–71], empirical data on the scope, magnitude, and epidemiology of diversion are largely unavailable and remain absent from the literature. In fact, at a recent meeting sponsored by the College on Problems of Drug Dependence focusing on the "Impact of Drug Formulation on Abuse Liability, Safety, and Regulatory Decisions", representatives from government regulatory

Table 3. Odds ratios of lifetime non-medical prescription opioid abuse/dependence and lifetime Diagnostic and Statistical Mental Disorders (4th edition) psychiatric disorders. Data were from 42 300 individuals from the US household population, interviewed as part of the National Epidemiologic Survey of Alcohol and Related Conditions.

Disorder	Odds ratio	95% confidence interval
Alcohol use disorder	11.4	8.6–15.1
Other non-medical prescription drug use disorder	80.1	58.7–109.1
Illicit drug use disorder	28.1	20.4–38.7
Nicotine dependence	6.7	5.3–8.5
Any mood disorder	4.6	3.6–5.9
Major depressive disorder	2.4	1.8–3.2
Bipolar I	4.9	3.6–6.6
Bipolar II	4.3	2.6–7.0
Dysthymia	3.0	2.1–4.2
Any anxiety disorder	3.0	2.4–3.8
Panic with agoraphobia	4.3	2.4–7.6
Panic without agoraphobia	4.0	3.0–5.3
Social phobia	2.4	1.7–3.6
Specific phobia	2.3	1.7–3.1
Generalized anxiety	2.7	2.0–3.7
Antisocial personality disorder	8.1	6.2–10.6

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agencies, the pharmaceutical industry, and the research community agreed the following [61,62,64,72–76]:

- There are no data on the magnitude of particular types of diversion.
- There are no systematic data on how the massive quantities of abused prescription drugs are reaching the streets.
- There are no empirical data that might be used for making regulatory decisions and for developing prescription drug prevention and risk management plans.

In addition, although a number of studies have addressed the patterns of prescription drug abuse and diversion among healthcare professionals [48,77–80], little is known about the magnitude and mechanisms of diversion among current and former pain patients who abuse prescription opioids.

Prescription opioid abuse and psychiatric comorbidity

Recent epidemiological evidence clearly demonstrates elevated rates of a spectrum of psychiatric disorders in individuals reporting lifetime use of, or abuse/dependence on, prescription opioid medications. Specifically, Huang et al. analyzed data

Table 4. Demographics of national prescription opioid abusers in the USA.

	Total n=1408	Male n=773	Female n=605
White race	85.48%	88.85%	81.49%**
Prior number of times treatment sought	3.05±0.24	3.42±0.38	2.70±0.31
Age at current treatment (years)	34.79±0.31	34.08±0.43	35.57±0.46*
Education			
Some college	50.53%	45.25%	57.63%**
Source			
Dealer	69.40%	74.03%	63.48%**
Forged prescription	10.15%	9.73%	10.93%
Stolen	23.47%	25.70%	21.18%
Doctor	62.86%	58.80%	66.98%**
Friend or relative	68.39%	66.45%	70.75%
Emergency department	29.03%	27.06%	31.33%
Internet	7.24%	7.80%	6.70%
Diagnosed abuse			
Alcohol abuse[1]	43.24%	43.16%	43.10%
Nicotine dependence[2]	69.36%	65.77%	73.61%
Age of first psychotropic use (years)			
Alcohol	14.39±0.17	14.31±0.22	14.52±0.25
Marijuana	14.52±0.34	14.73±0.17	15.14±0.28
First intoxication	14.93±0.16	15.18±0.53	13.93±0.43
Nicotine	16.49±0.27	16.42±0.38	16.52±0.39
Powdered cocaine/crack	20.82±0.91	24.29±2.46	20.35±2.00
Stimulants[3]	21.45±1.61	20.00±1.11	21.06±1.40
Benzodiazepines	21.88±1.36	19.79±1.56	23.64±2.02
Prescription opiates	22.32±0.47	21.63±0.69	23.00±0.66
Heroin	22.88±0.35	22.81±0.44	23.15±0.61
Heroin first opioid	8.77%	8.70%	8.33%

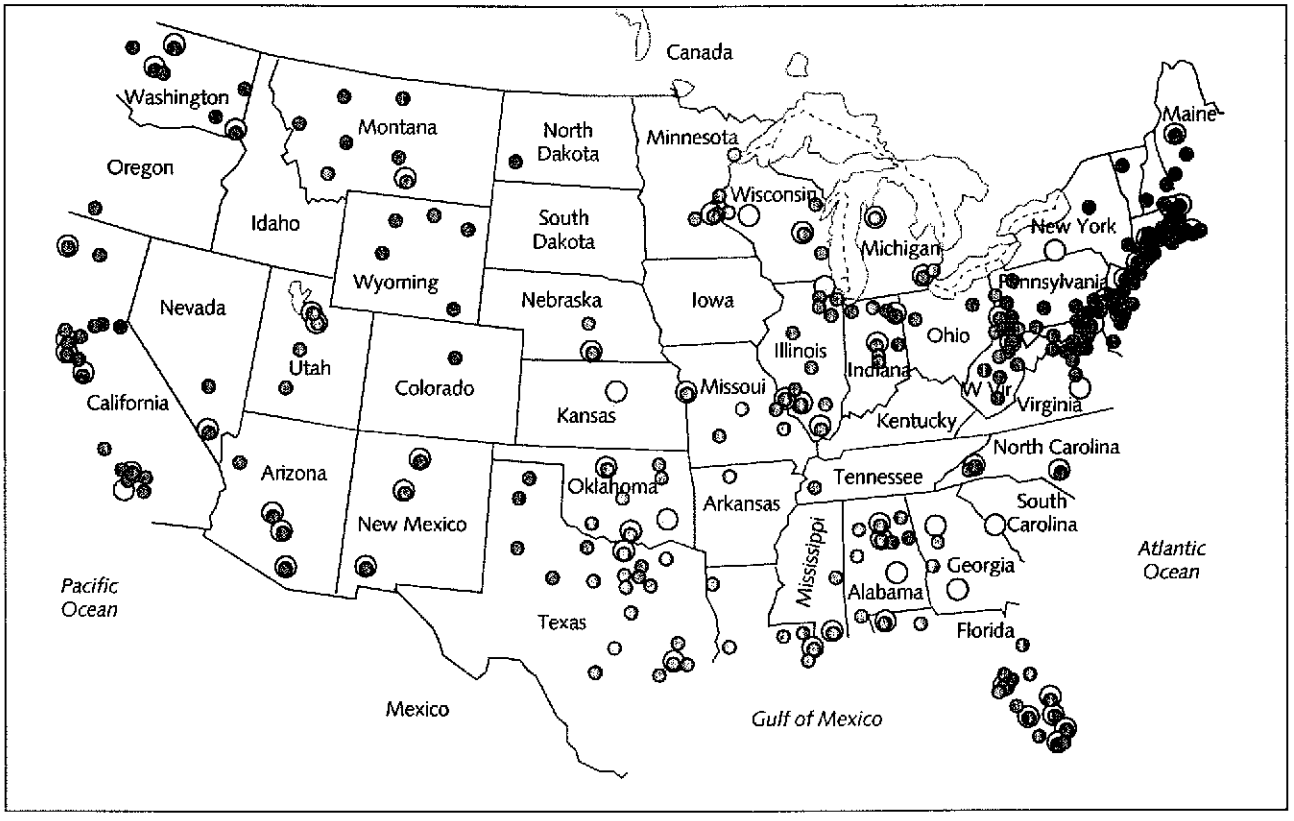
[1] Alcohol abuse as defined by the Diagnostic and Statistical Mental Disorders (4th edition) criteria.
[2] Nicotine dependence as defined by the Fagerström Nicotine Dependence Test [4].
[3] Stimulants include Adderall® (Shire US Inc., KY, USA), amphetamines, methamphetamines, and Ritalin® (Novartis Pharmaceuticals Corp., NJ, USA).
*Female results significantly different to males ($p<0.05$).
**Female results significantly different to males ($p<0.01$).

Table 5. Physical and mental comorbidity in national opioid abusers.

	Total	Male	Female
Chronic pain	61.48%	65.84%	57.65%
Self-reported pain score	5.41±0.14	5.39±0.20	5.38±0.21
Reason for first use – pain prescription	81.84%	79.23%	84.74%
Age of first use of opioid for pain (years)	21.91±0.49	21.51±0.72	22.27±0.68
First use of opioid for pain led to misuse	65.81%	62.18%	69.79%
Self-identified psychopathology	60.70%	54.73%	66.15%*
Depression	72.05%	68.14%	75.74%
Anxiety	55.29%	47.37%	61.03%*
Bipolar disorder	27.53%	23.85%	30.08%
Attention deficit disorder	14.92%	17.12%	12.12%
Other	10.79%	11.32%	10.00%

*Female results significantly different to males ($p<0.05$).

Figure 3. Location of opioid abuse treatment centers (grey circles) and patients who completed questionnaires (red circles).



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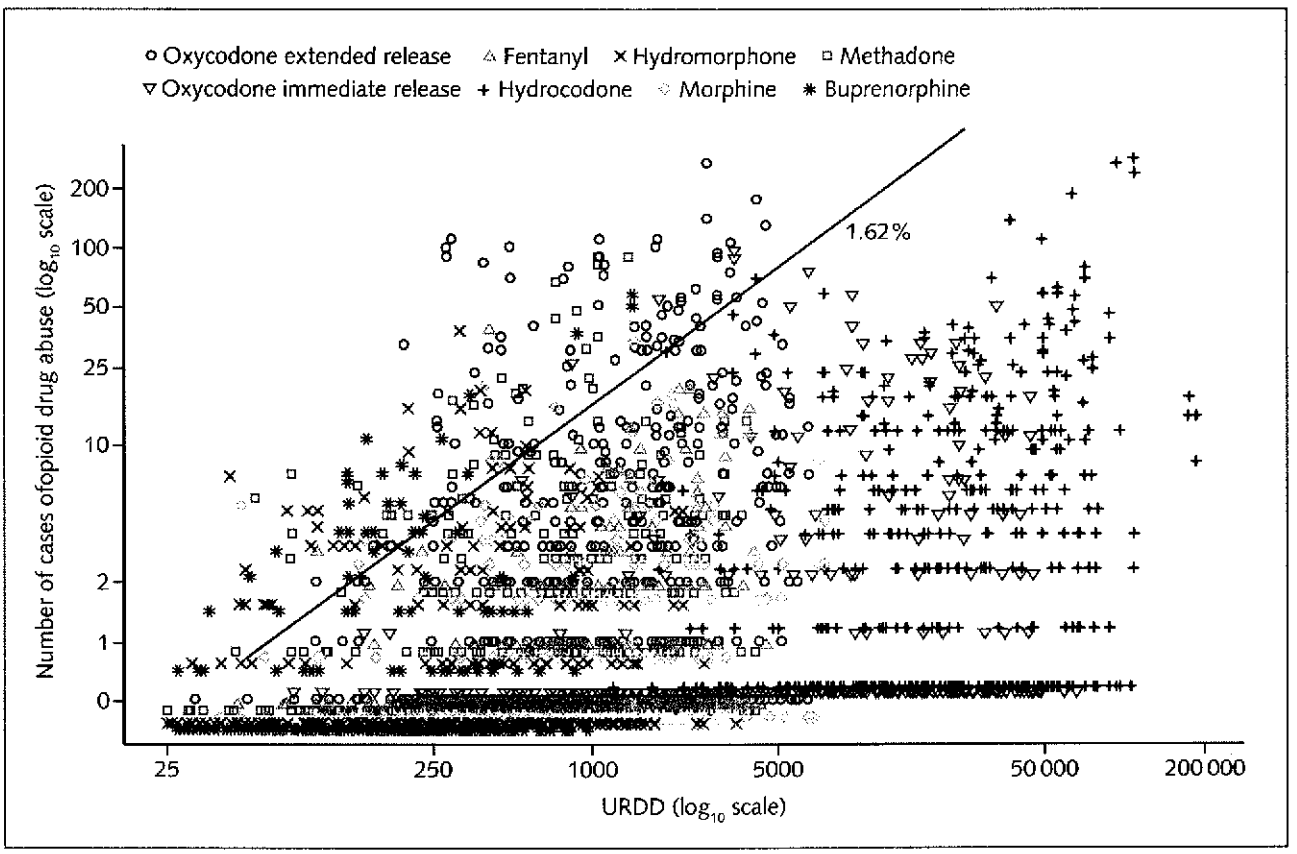
from 42 300 individuals from the US household population [81], interviewed as part of the National Epidemiologic Survey of Alcohol and Related Conditions [82,83]. Their analyses, summarized in Table 3, indicated dramatically elevated odds of other drug use disorders, antisocial personality disorder, and mood and anxiety disorders. While information from large-scale samples of individuals seeking treatment for prescription opioid abuse/dependence, treatment referral biases [84,85] and other factors suggest that rates of these disorders may actually be further elevated in those seeking treatment. For example, as shown in Tables 4 and 5, data from our own ongoing studies [86] suggest elevated rates of both poor mental health and poor physical health in individuals receiving treatment for opioid abuse/dependence. These data are important in that they can be used by pain management specialists as a benchmark against which to judge whether a pain patient requiring opioid therapy is an "at-risk" individual whose medications should be monitored closely.

Relationship between use and abuse

From the foregoing data on the history of prescription drug abuse, it is easy to assume that, in the face of constant levels of therapeutic use of opioid analgesics for pain, there has been a disproportionate increase or epidemic of prescription opioid abuse. Is this true? From a recent study, we conclude that the answer is no.

To address this issue we established a network of opioid abuse treatment centers (Fig. 3) who agreed to give detailed questionnaires to each of the first 50 consecutive patients treated. The zip code locations of the patients completing the questionnaire are also shown in Fig. 3. From these surveys, we ascertained the number of individuals who used specific opioid analgesics to "get high" in the past 30 days. We also had access to the overall number of people completing a prescription for each opioid in the same postal zip code in which the patient lived, in order that the number of abuse cases occurring in a given zip code relative to the number of people filling a prescription could be calculated. From the collated data, we then plotted therapeutic exposure against the number of abuse cases for eight different opioid drugs (Fig. 4). There was a strong correlation between therapeutic exposure to opioid analgesics – as measured by prescriptions filled – and their abuse. However, there were geographical loci that represented outliers in which abuse was

Figure 4. Relationship between abuse cases and URDD from the second quarter of 2005 to the first quarter of 2006. The 95th percentile is shown by a line. The 1.62% refers to the rate of abuse (cases per 1000 unique recipients of dispensed drugs) above which were the 5% outliers.



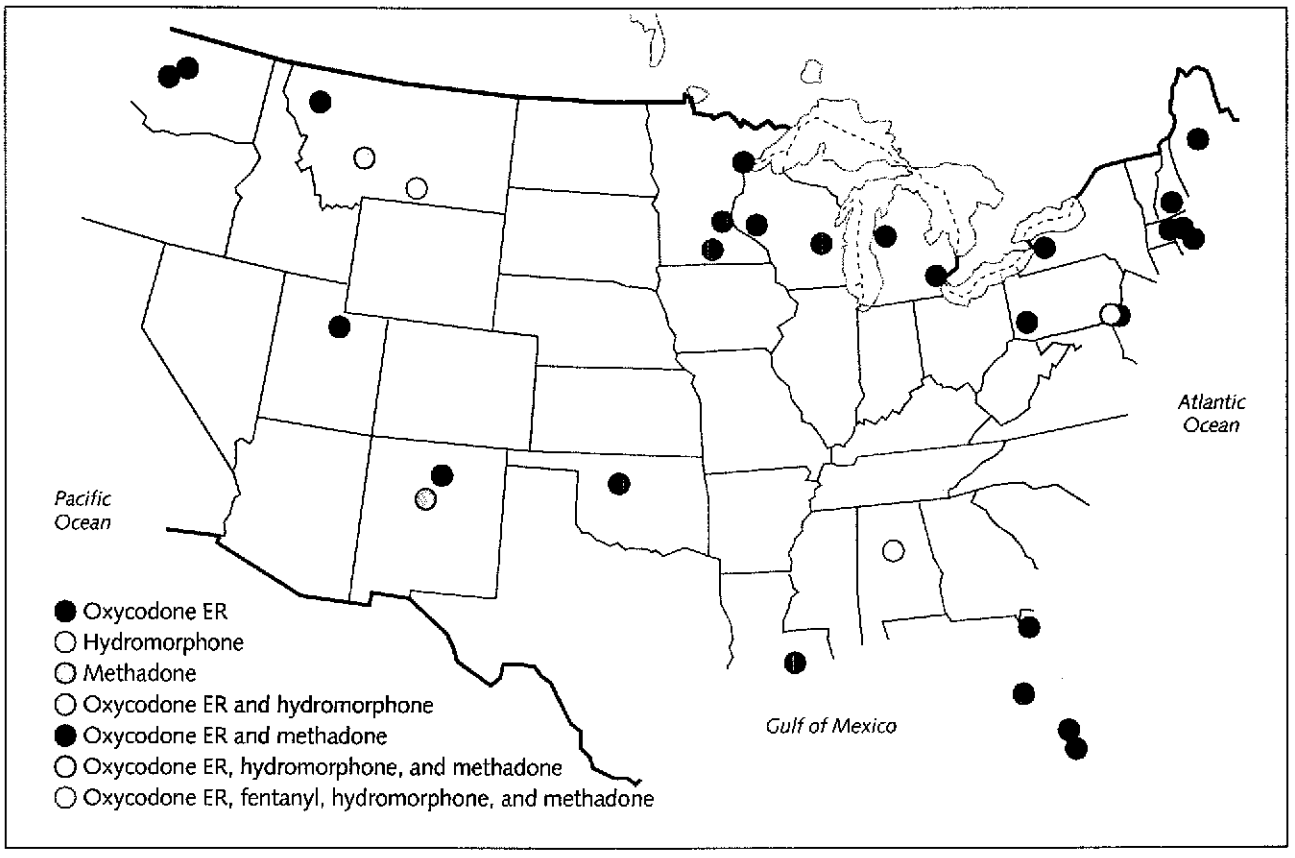
URDD: unique recipients of dispensed drugs. Redrawn with permission from [95]. Copyright © (2007) John Wiley & Sons Limited.

disproportionately high relative to therapeutic use (>95th percentile). The 95th percentile is shown by a line in Figure 5. The 1.62% refers to the rate of abuse (cases per 1000 unique recipients of dispensed drugs) above which were the 5% outliers. Most of the outliers were in very small urban, suburban and rural areas.

Our data indicate that there is a statistically significant ($p<0.05$) correlation between legitimate, therapeutic exposure to opioid analgesics, and the magnitude of abuse. While this seems logical and intuitive, the relationship has only been inferred previously [87]. Clearly, this indicates that in areas in which a drug is widely used for therapeutic purposes, there is unfortunately a coincident increase in availability to those who use drugs non-therapeutically (e.g. to "get high"). It seems reasonable to assume that a small percentage of every opioid drug prescribed is diverted and used non-therapeutically. Thus, if large quantities of drug are prescribed, the actual numbers of cases of abuse will rise accordingly simply on the basis of mathematical projections. This postulate assumes that the value of a drug for non-therapeutic purposes determines the level of diversion and, as a result, the relative rates of abuse for specific opioid analgesics reflect their abuse liability. It is further assumed that the rate of abuse will remain constant across the country (i.e. abuse rates closely track exposure). If this is true, then if a specific area of the country has disproportionately high levels of abuse, this would suggest that certain region-specific factors make this area unique.

The fact that there are "signals" of high abuse in discrete loci is not new. It has been shown for decades that prescription drug abuse (opioids, sedatives, and stimulants) is indigenous to certain areas [88–91], including the northeast, and that "epidemics" of abuse often appear suddenly in as few as three to five cities, and then quickly dissipate. It is noteworthy that the "signals" of abuse identified in our studies – while present to some extent in larger cities – are for the most part concentrated in small- to medium-sized urban, suburban, and rural areas. The reasons for this are unclear, but several

Figure 5. Areas of the country in which there were 1–4 signals of disproportionately high abuse for any of eight opioid analgesics examined.



ER: extended release. Redrawn with permission from [95]. Copyright © (2007) John Wiley & Sons Limited.

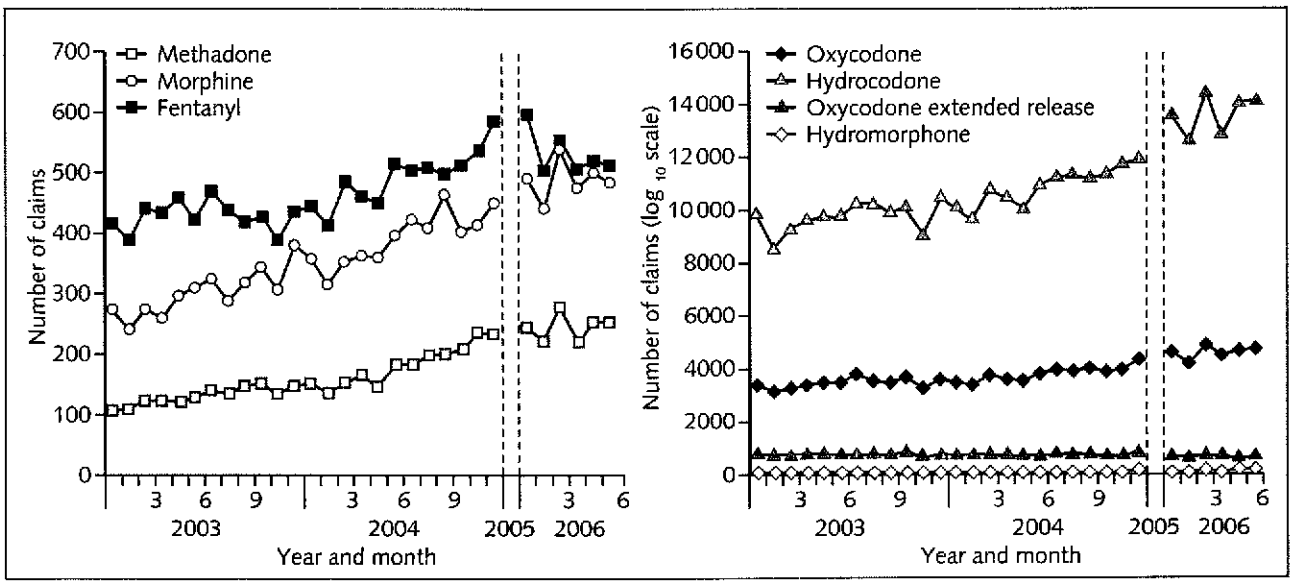
prominent possibilities exist, as suggested in earlier studies [92,93]. Firstly, very cheap heroin is often not readily available in non-urban areas; secondly, prescription drug abuse has been indigenous for decades in some rural areas [88–91]; thirdly, prescription drugs are often viewed as "legal", more socially acceptable, and can be obtained relatively easily in much safer locations than heroin; and finally, the cost of prescription drugs at US$1–2/mg may be less of an obstacle to their use in suburban, small urban, and rural areas than it is in the inner cities where financial resources are more limited.

There are other explanations for the regional disparity in signal sites, which may reflect an inherent bias in our studies, and thus limit the conclusions. Specifically, we did not have informants in a large number of states (e.g. Idaho, South Dakota, Kentucky and Iowa) or there was overrepresentation in some areas and underrepresentation in others. This may have introduced an intrinsic bias in our study. In addition, other than methadone clinics or other free clinics, drug treatment facilities that require some form of payment may not be readily available in inner cities or may be financially inaccessible for many abusers. However, since nearly half of our treatment centers were located in zip codes with very large populations, accessibility seems to be an unlikely factor in the regional disparity observed. Rather, the fact that signal sites were found in non-urban areas could reflect either that urbanites do not seek treatment for some reason (e.g. they are recreational users), or that the treatment facility was too expensive for the majority of those living in inner cities. While the latter seems most probable, it is not likely to be the sole explanation since treatment centers were located in cities with very large numbers of affluent people (e.g. the Manhattan borough of New York), but there were very low rates of abuse in those areas.

Is there an epidemic of prescription drug abuse?

While the abovementioned data suggest that there is a good correlation between areas where exposure is high and abuse, one direct question remains unanswered: is the increase in abuse over the past 5–10 years simply a reflection of increased exposure? To answer this, we examined the number of claims from a large insurance claims database

Figure 6. Number of insurance claims for the most common classes of opioid analgesics, by month.



covering 611 089 citizens of the state of Missouri from January 1, 2003–June 30, 2006 for the eight most common classes of opioid analgesics. Assuming that the extent of claims reflects use, it is apparent that there was significant growth in the use of most opioid drugs that are given for chronic pain (Fig. 6), suggesting that the efforts to encourage physicians to adequately treat pain with opioid analgesics may have been productive. As a consequence of this increase in therapeutic use, one would predict that the number of abuse cases would also rise; however, if one was to correct for exposure, the rate (expressed as cases of abuse per 1000 persons filling a prescription) would remain flat or exhibit only a slight upward trend. Thus, we believe that there has not been a steady disproportionate rise in prescription opioid abuse, but that much of the increase in abuse of prescription opioids over the last 10 years simply reflects that a certain small percentage of the rising number of opioids used therapeutically are diverted for non-therapeutic purposes. We consider this to be a subtle but very important point, which does not diminish the importance of understanding prescription drug abuse that has certainly risen, but places this abuse into a rational framework.

Conclusion

Although there has been an upsurge in the abuse of prescribed opioid analgesics over the past decade, we believe that much of this increase is due to an equally prominent surge in the therapeutic use of these drugs. That is, if a small percentage of opioids used therapeutically are diverted for non-therapeutic purposes, and if this is held constant, then naturally the incidence of abuse will increase as therapeutic availability increases. Nonetheless it is apparent that the rate of abuse of prescription opioids has increased slightly more rapidly than can be predicted solely on the basis of the considerations outlined above. It seems that those most prone to abuse have an extensive degree of physical disease, particularly psychopathology. Given the characterization of those at risk of abuse, physicians should be able to recognize such individuals and use opioids carefully in this group. Moreover, given the intrinsic comorbidity in chronic pain patients, it is clear that any comprehensive pain management program should treat not only pain and the underlying physical disease state causing the pain, but other comorbid physical and psychiatric conditions as well. Furthermore, given the pharmacological complexity of managing pain with opioids, the involvement of pain management specialists in the treatment plan for most of those in chronic pain would seem pertinent in order for optimal treatment to be provided.

Disclosures

The author has no relevant financial interests to disclose.

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CASE STUDY

Acute Pain Management in the Emergency Department for Patients on Methadone Maintenance: A Case Study

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Pain is a common reason for emergency department visits and patients with histories of substance abuse are overrepresented in the emergency department population. The management of patients on methadone maintenance therapy who present to the emergency department with acute pain resulting from illness or injury is particularly complex. This case study examines the care of a patient receiving methadone maintenance therapy who presented to the emergency department after suffering a tibial plateau fracture. In this case study we identify potential pitfalls in therapy and offer recommendations for pain treatment that should result in optimal outcomes. *Adv Pain Manage* 2008;**2**(1):30–2.

Case study

A 35-year-old African American male presented to the emergency department (ED) after suffering a fall while playing basketball. Immediately after the fall, the patient experienced pain in the left knee and has been unable to bear weight. Upon consultation, he reported a pain intensity score of "11" on a 0–10 scale, resisted all efforts to examine his knee, and demanded intravenous opioids. At this time, efforts to elicit additional past medical history were unsuccessful. The emergency physician then ordered a dose of intramuscular ketorolac 30 mg and a radiograph for the involved extremity. At 15 mins after receiving the ketorolac, the patient relayed that he had a past history of intravenous heroin abuse and was receiving oral methadone 100 mg/day through his methadone maintenance treatment program, but had missed his daily dose. He could not produce documentation of his methadone regimen. The radiograph of the knee revealed a complex tibial plateau fracture and the consulting orthopedic surgeon advised surgical intervention. The patient insisted that he should be given methadone; however, the emergency physician refused and administered repeated small doses of intravenous morphine for minimal relief of pain while the patient remained in the ED awaiting an inpatient hospital bed. The patient's demands for methadone became increasingly loud and insistent as the night progressed.

The patient was ultimately admitted to the orthopedics floor and the acute pain service was consulted the following morning. By then, the patient's methadone regimen was confirmed and his usual daily methadone dosing was resumed. The patient's pain was initially poorly controlled, but was ultimately managed successfully with combined ketorolac, ketamine, hydromorphone patient-controlled analgesia, and a continuous femoral nerve block. He underwent operative repair without incident and was maintained on his usual methadone dose throughout his hospital stay.

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Discussion

Pain is the most common reason for seeking healthcare and accounts for approximately 78% of the presenting complaints of visitors to the ED [1–3]. Adequate analgesia is an important goal in the treatment of pain; however, the underuse of analgesics, termed "oligoanalgesia," occurs in a large proportion of ED patients [4,5].

The ED frequently treats patients with histories of substance abuse, both active users and those in treatment. In 1996, Rockett et al. used direct interviews of adults presenting to seven Tennessee, USA EDs in a statewide probability sample survey to ascertain unmet substance abuse treatment needs [6]. Although only 1% of ED medical records indicated a diagnosis of alcohol- or drug-related problems, approximately 27% of patients were considered to need substance abuse treatment according to the researchers, who came to this conclusion based on explicitly defined case definitions; <10% of these patients were actually receiving such care. Of all the patients in this study, 32% screened positive in saliva or urine assays for psychoactive drugs and 9% were positive for opioid use.

Unmet substance abuse treatment needs correlated directly with the frequency of ED visits and inversely with patient age.

Given the prevalence of pain and substance abuse among ED patients, it is not uncommon that emergency physicians will treat patients who present with acute pain resulting from injury or illness and receive opioid agonist therapy (i.e. methadone) as part of their treatment for opioid addiction. The management of these patients can be complicated by a number of factors, including mutual medical mistrust (of patient by physician and of physician by patient), misconceptions regarding the analgesic properties of methadone when used as maintenance therapy, and fear that using short-acting opioids for pain control may increase the likelihood of addiction relapse. In addition, emergency physicians practice at a marked disadvantage in comparison to the continuity physician. Basic information about past medical or social history may be unavailable and the emergency physician is rarely kept informed of a patient's outcome after discharge. Treating complex psychosocial problems as well as pain in such an information vacuum presents a distinct challenge to the emergency physician.

Aside from considerations involving methadone maintenance therapy, members of ethnic minorities are at risk for inadequate treatment of pain in the ED, even in those who are suffering from acute pain due to an obvious cause (e.g. fracture). The first reports of such ethnic disparities in analgesic prescribing came from the ED of UCLA in Los Angeles, USA in 1993, where Hispanic patients with extremity fractures were found to be twice as likely as non-Hispanic white patients to receive no opioid analgesics [7]. Later studies from the Emory University in Atlanta, USA found similar disparities between African American and non-Hispanic white patients regarding analgesic treatment for fractures [8]. In both of these studies, such disparities persisted after controlling for multiple possible confounders.

More recently, Pletcher and colleagues assessed data from the National Hospital Ambulatory Medical Care Survey and reported that although opioid prescribing for pain-related ED visits increased markedly in 1993–2005, differential prescribing based on ethnicity persisted and was more pronounced with increasing pain intensity [9]. They also report that, on average, opioids were prescribed during 31% of pain-related visits by non-Hispanic white patients compared with 23% of visits by African American patients and 24% by Hispanic patients. By 2005, opioids were prescribed for 40% of non-Hispanic white patients compared with 32% for all other ethnic groups. Differential opioid prescribing for non-Hispanic white and African American patients was seen for long-bone fractures (52% vs. 45%) and nephrolithiasis (72% vs. 56%), two conditions for which an objective cause of severe pain is evident.

Mutual medical mistrust in the setting of active or relapsed opioid addiction is a common phenomenon. In the present case study, an African American patient undergoing methadone maintenance therapy was viewed by the emergency physician as manipulative and demanding. It is likely that the patient's history of opioid abuse served to stigmatize him in the eyes of the physician and the distinction between an appropriate request for potent analgesics and manipulative drug-seeking behavior was blurred, even in the setting of an obvious etiology of pain. This phenomenon is a none-too-subtle form of pseudoaddiction, as evidenced by the eventual success of aggressive, multimodal pain management by the acute pain service [10].

In addition to the pain associated with his tibial plateau fracture, the patient may have experienced early opioid withdrawal symptoms, or, more likely, the fear of impending withdrawal symptoms. This caused an increase in the patient's pain-associated anxiety and resulted in escalating demands for opioid treatment. In such cases, the physician should reassure the patient that adequate pain treatment is the goal of care. Aggressive titration of short-acting intravenous opioids should be pursued. Given the potential for drug interactions and production of active metabolites, frequent boluses of hydromorphone or fentanyl titrated to pain relief are preferred to morphine. Mixed agonist/antagonist opioids, such as nalbupine, butorphanol, or pentazocine are contraindicated as they may cause acute opioid withdrawal.

Verification of the patient's participation in a methadone maintenance program as well as his daily methadone dose is difficult to obtain in the ED outside of normal business hours. Although it is important to continue the patient's usual methadone regimen with the least possible interruption, verification of the patient's dose may not be possible until the next day. The physician should understand that methadone used for maintenance purposes does not provide sustained analgesia. Methadone has a relatively short analgesic half-life (4 h) compared with the duration of its withdrawal-prevention effects (24–48 h). In general, the patient undertaking methadone maintenance therapy will require much higher doses of opioid to achieve analgesia in the setting of an acutely painful injury. Opioid tolerance resulting from long-term methadone use can also cause cross-tolerance to other opioids, thus to obtain adequate analgesia, higher and more frequent doses of a short-acting opioid will be required [11]. The role of opioid-induced hyperalgesia is less clear in this setting; however, increased pain sensitivity in patients undergoing long-term opioid agonist therapy has been observed under experimental conditions [12].

Physicians may fear that aggressive opioid administration raises the risk of a relapse in substance abuse patients. Although short-acting opioids have the potential to induce euphoria and increase drug craving, in the setting of acute pain there is little evidence to suggest that their use is associated with relapse. In fact, it has recently been suggested that uncontrolled chronic pain is the more worrisome risk factor for resumption of recreational drug use as well as social isolation [13].

Although ED care should involve attempts to verify and re-institute methadone dosing while aggressively titrating short-acting opioids in order to achieve pain relief, the inpatient and perioperative phases of care provide a number of opportunities for advanced pain management strategies. Patient-controlled analgesia allows the patient to exert control over pain and may decrease pain-associated anxiety. In cases in which the patient displays relatively poor responsiveness towards opioid analgesics, multimodal therapies, including peripheral continuous nerve block, nonsteroidal anti-inflammatory drugs, ketamine, and intravenous lidocaine may be useful as alternative treatments. For particularly challenging cases, addiction specialists should be involved in the patient's care.

Conclusion

A number of considerations for acute pain treatment, particularly in the ED, in the setting of methadone maintenance therapy have been identified in this case study. Patients undergoing such therapy are at increased risk for undertreatment of pain and uncontrolled pain may increase the risk of substance abuse relapse. Uninterrupted methadone therapy, aggressive short-acting opioid analgesic titration, and consideration of multimodal therapies should lead to optimal outcomes.

Disclosure

Dr Todd has received consultancy fees for Abbotts Labs, Alpharma, and Johnson & Johnson.

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CLINICAL REVIEWS

Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Lara Dhingra, PhD and Helena Knotkova, PhD

NEUROPATHIC PAIN

Pain in hereditary neuromuscular disorders and myasthenia gravis: a national survey of frequency, characteristics, and impact

Guy-Coichard C, Nguyen DT, Delorme T et al.
J Pain Symptom Manage 2008;**35**:40–50.

The authors of this article conducted a survey on a sample of 511 French patients suffering from neuromuscular disorders (NMDs) with the intention of studying their pain characteristics. The results of the survey showed that these patients frequently experience chronic pain, and that this may be the main problem affecting their quality of life. Pain in subjects with NMDs should be routinely and systematically assessed.

This well-coordinated, large, multicenter study used a survey to evaluate the characteristics of pain in patients suffering from neuromuscular disorders (NMDs). The pathologies assessed were the three main categories of muscular dystrophy, the metabolic myopathies, and myasthenia gravis. As the nature of these disorders creates an objective clinical focus on motility, the subjective experience of pain – either spontaneous or as a result of medical interventions – tends to be underestimated. This is likely to be compounded by the major pulmonary and cardiac risks that can occur as a result of pain management interventions. The present study is focused on recollections during the prior 3 months regarding issues of:

- Pain frequency.
- Pain intensity.
- Pain duration.
- Impact of pain on functioning.

The data regarding pain management perceptions and drug utilization collected in this survey are to be presented in a separate publication.

Pain was reported to have occurred during the previous 3 months by 67% of the patients. It occurred for ≥30 days in 36% of patients. The average number of days with pain was 18 days of the 3-month period. While the average intensity of pain (according to the classification adapted from [1,2]) was graded as 4.8/10, it was ≥7/10 in 27% of patients. Those with metabolic myopathies had the highest frequency (79.5%) and intensity (49% with an intensity of ≥7/10). Interestingly, while patients with myasthenia gravis had a relatively low frequency of pain, they scored relatively highly in terms of intensity scores. Pain duration was predominantly intermittent but lasted >1 day in 47% of patients assessed, and for >2 days in 38%. The more severe pain had the longest persistence.

Prolonged inactivity due to pain was infrequent; the number of days of inactivity was closely related to pain intensity. While 74% had fewer than 10 days of inactivity due to pain, there was a small subgroup that was highly incapacitated and inactivity correlated with pain intensity in this group. Leisure activities and activities of daily living were the factors that were most impacted by pain. Mood changes closely followed.

This study demonstrated the highest severity and impact of pain in the metabolic myopathy group. However, there was significant variability, with a high pain frequency in one category of muscular dystrophy (fascioscapulohumeral muscular dystrophy), and high reporting of intense pain in the myasthenia gravis group.

Physical factors influencing pain were reported. These were quite variable in response, with notable pain relief obtained by massage and physiotherapy in 85% and 80% of responses, respectively.

The authors present compelling data to support the systematic assessment of pain in patients with NMD to achieve the goal of pain management as part of comprehensive care for this group. The limitations of this study are due predominantly to the subjective and retrospective assessments made in the written questionnaires. The addition of objective medical observations would provide considerable information to the present data. Furthermore, the lack of self-reported or

observed impact of psychological variables limits the application of important therapeutic interventions.

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Neuropathic pain: are there distinct subtypes depending on the aetiology or anatomical lesion?

Attal N, Fermanian C, Fermanian J et al.
Pain 2008;Advance online publication.

This study investigated associations between neuropathic pain symptoms, etiologies, pain localization, and type of nerve lesion. In addition, the authors examined the internal structure of the Neuropathic Pain Inventory. A total of 482 patients participated in this study. The results showed that there were more similarities than differences in the neuropathic positive symptoms associated with various lesions. Therefore, etiologically diverse groups of neuropathic pain patients can be grouped into a specific multidimensional category for the purpose of therapeutic management.

Neuropathic pain is characterized by a number of symptoms that can be classified as either positive (e.g. burning pain, electric shocks, dysesthesia, and allodynia) or negative (particularly sensory deficits). The present authors have recently shown that positive neuropathic symptoms are associated with distinct dimensions including deep pain and evoked pain [1]. However, it was unclear whether the multidimensional nature of neuropathic pain is related to the etiology or to the location of the neural lesion. Thus, whether various etiologies are associated with specific combinations of symptoms of neuropathic pain, or whether symptoms are similar regardless of the etiology remained to be determined.

In this study, associations between neuropathic pain symptoms, etiologies, pain localization, and type of nerve lesions were investigated. Symptoms and dimensions were assessed using a specific questionnaire, namely, the Neuropathic Pain Inventory (NPSI). The investigators used a multivariate statistical method (multiple correspondence analyses) to determine the associations between neuropathic positive symptoms and etiologies, and locations and varieties of neural lesions. A pool of 482 patients with pain attributed to a primary lesion of the peripheral or central nervous system participated in the study. The NPSI inventory, which includes 10 symptoms commonly associated with neuropathic pain (e.g. burning, pressure, tingling), was administered to all patients. In addition, 90 randomly selected patients underwent sensory testing. Multivariate statistical analyses revealed that neuropathic symptoms as described by the NPSI can be categorized into five dimensions:

- Evoked pain.
- Pareshesia/dysesthesia.
- Deep pain.
- Paroxysmal pain.
- Burning pain.

In addition, it was shown that there were only few associations between symptoms (dimensions) and etiologies, types of lesion, or pain localization. Exceptions included idiopathic trigeminal neuralgia and postherpetic neuralgia. These findings indicated that there were more similarities than differences in the neuropathic positive symptoms associated with various peripheral or central lesions. The results provide rationale for the grouping of etiologically diverse population of neuropathic pain patients into a specific multidimensional category for therapeutic management.

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Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double-blind study

Frank B, Serpell MG, Hughes J et al.
BMJ 2008;**336**:199–201.

In this study, the analgesic efficacy and side effects of the synthetic cannabinoid nabilone were compared with the weak opioid dihydrocodeine for the treatment of chronic neuropathic pain. The study consisted of 96 patients who received a maximum daily dose of dihydrocodeine 240 mg or nabilone 2 mg at the end of each titration period. The results showed that dihydrocodeine provided better pain relief than nabilone and had fewer side effects.

Nabilone is a synthetic cannabinoid that exerts its effect by interacting with cannabinoid receptors 1 and 2, and is used for treating chemotherapy-induced nausea and vomiting. Studies in animal models of neuropathic pain have indicated a potential role of cannabinoids in the treatment of neuropathic pain, and a study in patients with refractory chronic pain conditions who were treated with nabilone

showed beneficial effects [1]. The aim of this randomized, crossover, double-blind study was to compare the analgesic efficacy and safety of nabilone with dihydrocodeine, a weak opioid used for the treatment of chronic pain. As noted by the authors, dihydrocodeine is a good comparative agent owing to its psychotropic and sedative side effects.

A total of 96 patients with chronic neuropathic pain, from three outpatient facilities in the UK, participated in this study. Patients were randomized to first receive either treatment with nabilone or with dihydrocodeine in the following protocol: 1 week of baseline, 6 weeks of the first drug, 2 weeks of washout, 6 weeks of the second drug. The primary outcome measure was pain score using the visual analogue scale (VAS; 0–100 mm). The study drugs were given in escalating doses over the 6-week period, starting from dihydrocodeine 30 mg or nabilone 250 µg to a maximum daily dose of 240 mg or 2 mg, respectively, at the end of each 6-week titration period. If the patient developed side effects, the dose was reduced to the previous level.

The results showed that dihydrocodeine resulted in significantly better pain relief than nabilone. Clinically significant pain relief (i.e. a drop in VAS score of >10 mm) was observed in 12 patients with dihydrocodeine, while three patients responded well to nabilone. No patient responded to both of the investigated drugs, and 49 patients had no clinically significant pain relief with either treatment. The side effects seen with both treatments were mild, but fewer side effects were reported during treatment with dihydrocodeine.

As pointed out by the authors, the findings from this study indicate that efficacy of nabilone in neuropathic pain is, at best, modest. However, these findings are a relevant contribution to the debate on cannabionid use for pain management.

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Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial

Nurmikko TJ, Serpell MG, Hoggart B et al.
Pain 2007;**133**:210–20.

In this randomized, placebo-controlled trial, sativex – an oro-mucosal analgesic formulation based on cannabis extract – reduced allodynia and sleep disturbances in patients with neuropathic pain of varying etiology.

There is a well-recognized need for more efficacious pain relief medication than the currently available therapies. Alleviating neuropathic pain is especially challenging, with no more than 40–60% of patients achieving partial relief [1]. Sativex is a recently developed endocannabinoid system modulator for adjunctive analgesic treatment of pain. The drug is derived from extracts from the cannabis plant and is used as a spray formulation for sublingual and oro-pharyngeal administration. The principal active ingredients are Δ-9-tetrahydrocannabinol and cannabidiol. The current report describes a 5-week randomized, double-blind, placebo-controlled parallel-group study that evaluated the efficacy of sativex in relieving pain, allodynia, and sleep disturbances in patients with peripheral neuropathic pain.

A total of 125 patients, with peripheral neuropathic pain of varying etiology, were randomized to receive either active drug (n=63) or placebo (n=62). Following initial dosing under clinical supervision, a self-titration regimen was commenced. All patients continued their previous analgesic medication and used the study treatment concomitantly as and when needed, up to a maximum of eight sprays per 3-h interval or 48 sprays per 24 h.

At the end of the trial, the mean numerical rating scale (NRS) scores of reduction in intensity of global neuropathic pain (primary outcome measure) were –1.48 points (22% reduction) in the sativex group and –0.52 points (8% reduction) in the placebo group (p=0.004). The Neuropathic Pain Scale composite score and sleep disturbance NRS score (secondary outcome measures) were also significantly more reduced in the sativex group than the placebo group (p=0.007 and 0.001, respectively). The majority of adverse events (AEs) were gastrointestinal, central nervous system-related, or topical, and were mostly mild and recorded at the onset of treatment. However, six patients (10%) receiving sativex experienced multiple gastrointestinal AEs that were not reported by the placebo-group patients, including nausea, vomiting, diarrhea, and constipation. Withdrawals from the study due to AEs comprised 11 subjects receiving sativex (18%) and two receiving placebo (3%).

This study demonstrates that sativex has a broad efficacy in the treatment of neuropathic pain when used in addition to existing analgesic medication. Following the encouraging early results, the authors conducted an open-label extension study subsequent to the initial trial, providing 52-week data that showed maintained pain relief with no need for dose escalation.

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Differential changes in TRPV1 expression after trigeminal sensory nerve injury

Kim HY, Park CK, Cho IH et al.
J Pain 2008;**9**:280–8.

Previous studies in a trigeminal neuropathic pain model in rats have shown that pain hypersensitivity did not correlate with neuronal loss in trigeminal ganglion (TG). In this study, the authors examined changes in expression of transient receptor potential vanilloid 1 (TRPV1) in the injured compared with uninjured TG neurons. The results showed the upregulation of TRPV1 in uninjured TG neurons. The authors concluded that this receptor may play an important role in hyperalgesia observed after trigeminal nerve injury.

Although transient receptor potential vanilloid 1 (TRPV1) is believed to serves as a noxious heat sensor, this receptor is essential for the development of thermal hypersensitivity during inflammation and has also been implicated in the development of injury-induced neuropathic pain. Using a trigeminal pain model in rats, the authors aimed to investigate whether TRPV1 expression would be altered in injured compared with uninjured trigeminal ganglion (TG) neurons. The trigeminal pain model involved the inferior alveolar nerve and mental nerve transection branches of the mandibular trigeminal nerve.

The study rats were randomly assigned to receive transection surgery (n=24), sham surgery (n=3), or no procedure (healthy control animals; n=6). Injured TG neurons were identified using positive immunoreactivity for activating transcription factor 3, and TRPV1 expression was detected using immunohistochemical analysis at 3 and 60 days after surgery. In addition to the mandibular nerve, the analysis was performed in the TG neurons of the maxillary nerve, which was not transected.

Interestingly, the results showed that the expression of TRPV1 was increased significantly more in the uninjured mandibular TG neurons and in the uninjured maxillary TG neurons at 3 days after surgery, than in the injured neurons. At 60 days after surgery, no TRPV1 upregulation was observed, as TRPV1 expression had returned to basal level. These results demonstrate that injury of the trigeminal sensory nerve induceds differential changes in the expression of TRPV1, which suggests that TRPV1 may play an important role in the development of hyperalgesia following neural injury. Thus, TRPV1 might be a potential target in treatment of neuropathic pain.

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Topical amitriptyline versus lidocaine in the treatment of neuropathic pain

Ho KY, Huh BK, White WD et al.
Clin J Pain 2008;**24**:51–5.

This double-blind, randomized, crossover, placebo-controlled study evaluated the efficacy of topical 5% lidocaine and 5% amitriptyline to alleviate neuropathic pain in 35 patients with postsurgical neuropathic pain, postherpetic neuralgia, or diabetic neuropathy. Results showed that pain was significantly reduced by topical lidocaine, but not amitriptyline or placebo.

The tricyclic antidepressant amitriptyline has been shown to be effective in the treatment of many neuropathic pain conditions. Although oral administration of amitriptyline has been the gold standard for such conditions, titration to the higher therapeutic doses required to achieve adequate analgesia has been limited due to side effects associated with this drug.

The objective of this study was to compare therapeutic efficacy of topical 5% amitriptyline with an active agent (5% lidocaine) and placebo. A total of 35 patients with neuropathic pain participated in the study – eight patients with postherpetic neuralgia, 13 with postsurgical neuropathic pain, and 14 with peripheral neuropathy. All patients received amitriptyline, lidocaine, and placebo in random order. Participants were instructed to apply 3–5 mL of the drug twice daily for 1 week, and each treatment week was followed by a 1-week washout. The primary outcome measure was the reduction of pain intensity, measured using the Visual Analog Scale (VAS; using a 0–100 mm scale). The results showed a statistically significant reduction of VAS score, from 52.7±23.4 to 47.8±27.6, following lidocaine treatment. Amitriptyline and placebo did not significantly reduce pain scores.

As noted by the authors, it is not surprising that topical lidocaine was effective in reducing pain scores, as lidocaine patches are known to be effective for neuropathic pain. However, local application of amitriptyline did not show significant efficacy in the treatment of neuropathic pain. A limitation of the study was the short duration (1 week) of the study treatment. As comparison, a study in which topical doxepin was assessed for efficacy in neuropathic pain demonstrated significant pain relief only after 10 days of daily application [1].

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Characteristics and period prevalence of self-induced disorder in patients referred to a pain clinic with the diagnosis of complex regional pain syndrome

Mailis-Gagnon A, Nicholson K, Blumberger D et al.
Clin J Pain 2008;**24**:176–85.

This article reports on a case series of patients diagnosed with complex regional pain syndrome (CRPS) with self-induced symptoms. The authors conducted retrospective chart reviews of 175 consecutive neuropathic pain referrals and confirmed the diagnosis of CRPS in 11 men and 15 women. An evidence of active self-induced signs and symptoms were found in four female patients. These cases are presented in the article and compared with other similar cases seen by the authors in previous years.

The chart review of all cases of referred neuropathic pain, within a comprehensive pain clinic, was conducted over a period of 2 years. Of the 175 referrals, 41 patients were diagnosed with complex regional pain syndrome (CRPS). Application of the International Association for the Study of Pain (IASP) CRPS criteria confirmed the presence of CRPS in 11 men and 15 women. Of the 15 women, four displayed active self-induced signs and symptoms. Characteristics of these cases are described in the article, and compared with similar cases seen in previous years.

In the study sample, the period prevalence of self-induced disorders referred as CRPS included:

- 9.8% of all patients referred as CRPS.
- 15.4% of all patients fulfilling the 1994 IASP CRPS criteria.
- 26.7% of all women fulfilling the 1994 IASP CRPS criteria.

The authors suggest that the presence of the following symptoms should raise the index of suspicion for self-induced disorders in patients diagnosed with CRPS:

- Bizzare, migrating, symetrical, or well-demarcated cutaneous lesions.
- Severely demarcated swellings that are possibly associated with cutaneous lesions and/or ligature sign.
- Healing or disappearance of lesions and/or swelling under constant observation, casting, or after confrontation.

In addition, the presence of litigation or compensation should further add to the index of suspicion. However, the authors do not suggest that any of these factors constitute "criteria" for the diagnosis of self-induced disorder.

No patient in this study admitted to intentional self-injurious behavior for the purposes of assuming a sick role for financial or other purposes. However, the index of suspicion was high enough to warrant consideration of self-induced disorder, and the authors discussed the subject of self-inflicted abnormalities with most patients of the study. They suggest that no matter how high the clinician's index of suspicion is, it is important to be willing to address the situation with the patient, despite potential damage to the patient–clinician relationship or possible legal threats. Meticulous examinations, detailed documentation of all observations at each appointment, and use of still photographs, as well as communication with colleagues involved in the patient's care should be a part of best practice when managing cases involving high suspicion of self-induced disorder.

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Gabapentin prevents delayed and long-lasting hyperalgesia induced by fentanyl in rats

van Elstraete AC, Sitbon P, Mazoit JX et al.
Anesthesiology 2008;**108**:484–94.

In this study, subcutaneous administration of fentanyl in rats resulted in an early increase of nociceptive thresholds (i.e. analgesia) followed by a sustained decrease of nociceptive thresholds (i.e. hyperalgesia). Intraperitoneal or intrathecal administration of gabapentin did not significantly modify the early analgesic component, but prevented the delayed hyperalgesic component. The mechanism of prevention of opioid-induced hyperalgesia by gabapentin, at least partially, involves $\alpha_2\delta$ subunit of voltage-gated calcium channel.

Gabapentin has been shown to be effective for the treatment of neuropathic pain, and in reducing pain, allodynia, and hyperalgesia following tissue or nerve injury. Gabapentin acts by binding to the $\alpha_2\delta$ subunit of voltage-gated calcium channels. The aim of this study was to determine the effectiveness of gabapentin and the involvement of the $\alpha_2\delta$ subunit of voltage-gated calcium channels for the prevention of opioid-induced hyperalgesia (OIH), which develops following acute systemic administration of fentanyl in uninjured rats. OIH is a phenomenon observed after administration of various opioids; hence opioids do not only produce analgesia but can also cause enhanced pain sensitivity induced by central sensitization.

In this study, hyperalgesia was induced in the study rats by four subcutaneous injections of fentanyl (20, 60, or 100 μg/kg) administered at 15-min intervals. Intraperitoneal (30, 75, 150, or 300 mg/kg) or intrathecal (300 μg)

gabapentin was administered 30 min before or 300 min after the first fentanyl injection. Using the paw-pressure test, sensitivity to nociceptive stimuli was assessed at baseline, on the day of the experiment, and for 5 consecutive days after.

The results showed that gabapentin alone did not alter nociceptive thresholds. After administration of fentanyl, neither intraperitoneal nor intrathecal gabapentin significantly modified the early analgesic component of fentanyl, but both did dose-dependently prevent the delayed hyperalgesic component. Intrathecal administration of ruthenium red, known to modulate the binding of gabapentin to the $\alpha_2\delta$ subunit of voltage-gated calcium channels, partially but significantly diminished the preventive effect of gabapentin on OIH. This finding suggests that the preventive effect of gabapentin on OIH is at least partially mediated via voltage-gated calcium channels.

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Analysis of cerebrospinal fluid inflammatory mediators in chronic complex regional pain syndrome related dystonia

Munts AG, Zijlstra FJ, Nibbering PH et al.
Clin J Pain 2008;**24**:30–4.

A wide range of inflammatory mediators and other compounds are involved in the development and maintenance of chronic pain. As elevated levels of interleukin (IL)-1β and IL-6 were found in the cerebrospinal fluid (CSF) of patients with complex regional pain syndrome in a previous study, the authors aimed to confirm those findings and to search for additional CSF biomarkers.

The identification of biomarkers that are related to particular neurobiological pathways in complex regional pain syndrome (CRPS) may provide clues as to the pathogenesis of the disorder and may also contribute to an increased efficacy of therapeutic strategies. In a previous study, increased levels of interleukin (IL)-1β and IL-6 were observed in the cerebrospinal fluid (CSF) of patients with CRPS [1]. The aim of the present study was to replicate such findings and to identify additional CSF biomarkers in patients with both chronic CRPS and dystonia.

The authors compared CSF samples obtained from 20 CRPS patients with dystonia with samples from 29 control subjects. Within these samples, levels of IL-1β, IL-6, interferon-γ inducible protein-10, RANTES (regulated upon activation normal T-cell expressed and secreted), complement factor C3, mannose-binding lectin, complement Clq, soluble intercellular adhesion molecule-1, endothelin-1, nitric oxide, human lactoferin, and hypocretin-1 were assessed. The results showed no differences in the CSF levels in any of these compounds.

These findings do not support a role of inflammatory mediators in the development of chronic CRPS patients with dystonia. However, as the study sample involved CRPS in patients with long disease duration, a role of inflammatory mediators has not been excluded in the early stages of CRPS. Furthermore, aberrant neuroplasticity is considered to be the pivotal underlying mechanism of both neuropathic pain and dystonia. Thus, in patients with chronic CRPS, a search for CSF biomarkers involved in reorganization of central neural circuits may be more useful than a search for CSF levels of inflammatory proteins.

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Effect of anti-NGF antibodies in a rat tibia fracture model of complex regional pain syndrome type I

Sabsovich I, Wei T, Guo TZ et al.
Pain 2007;Advance online publication.

Using characteristics resembling those of patients with complex regional pain syndrome type I (CRPS I), the present authors created a rat model in which to assess the effect of nerve growth factor (NGF) on key features such as nociceptive sensitization, bone loss, warmth, and edema. Rats with fractured tibias were administered anti-NGF following injury and were assessed for nociception, bone loss, hindpaw warmth, edema, cytokine production, and other characteristics associated with CRPS I. The authors observed that anti-NGF is useful in reducing only some of the symptoms associated with this disorder.

In this study, the authors explored a rat model of complex regional pain syndrome type I (CRPS I) and investigated whether the use of anti-nerve growth factor (anti-NGF) might be a possible treatment for this disorder or at least helpful for some of its associated symptoms. The authors noted that tibia fracture in rats leads to allodynia, extremity warmth in the paw, regional osteopenia, and edema, and hence rats with such fracture were used as the animal model of CRPS I. In terms of treatment rationale, as NGF has been associated with increased nociception and neuronal changes, the authors hypothesized that anti-NGF might be useful in controlling the CRPS I features seen in the rat model.

To induce CRPS I, the distal tibia of the right hindlimb in rats was broken and set in a cast so that their hip, knee, and

ankle were kept in a flexed position for 28 days. Rats were injected with anti-NGF or vehicle at 17 and 24 days post-fracture. A control group receiving neither injection nor bone breakage was also observed. The authors tested for edema, extremity warmth, and nociception as outcomes. Although anti-NGF treatment did not result in changes in extremity warmth, edema, or cytokine production in the rats, it was found to be beneficial for reducing nociception sensitization and neuropeptide levels in the sciatic nerve. The authors conclude that CRPS I is a difficult pain problem to model and treat, but postulate that anti-NGF might be a useful intervention for at least some aspects of the disorder.

While this is a promising study, further validation work is necessary and eventual translation to humans is needed. In addition, although anti-NGF may someday have a role in the treatment of CRPS I, the solution to treating this highly complex disorder will still be incomplete. Finally, it would be interesting to see the impact of treatment at an earlier stage or immediately post-injury.

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Low-dose methotrexate reduces peripheral nerve injury-evoked spinal microglial activation and neuropathic pain behavior in rats

Scholz J, Abele A, Marian C et al.
Pain 2008;Advanced online publication.

The authors of this study investigated the use of methotrexate and dexamethasone in rats to determine whether these treatments are effective in reducing microglial responses to nerve injury. The results showed that low-dose methotrexate, administered at the time of injury, reduced microglial activity and pain-like behavior, whereas treatment with dexamethasone led to contrasting effects. The authors conclude that a feasible approach for preventing neuropathic pain may be found in suppressing microglial activation with an agent such as methotrexate.

Microglial proliferation is an important facet in understanding the development of neuropathic pain. Rats deficient in genes for activating spinal microglia have been shown to display reduced pain behavior in response to nerve injuries. Therefore, in this study, the authors aimed to determine whether such suppression could be achieved pharmacologically after induced nerve injury in a number of rat models.

To examine this question, rats were subjected to one of five conditions believed to offer a model of neuropathic pain:

- Spared nerve injury (SNI).
- Chronic constriction injury (CCI).
- Spinal nerve ligation (SNL).
- Rhizotomy.
- Sham surgery (control group).

Outcome was determined based upon the results of immunostaining, Western blots, enzyme immunoassays, and behavioral testing response to cold and mechanical allodynia. Overall, the authors found that in the SNI, CCI, and SNL models, the rats demonstrated consistent microglial activation. Furthermore, rats in these models – especially SNI – responded to low-dose methotrexate but not to dexamethasone, in terms of reducing microglial activation. In addition, the low-dose methotrexate group with SNI initially exhibited pain-like behaviors, but these behaviors remitted after 7 days of treatment, indicating some treatment or neuronal sparing impact of the drug.

This is a potentially important study for the pain field if the data hold up to replication and eventual translation to human studies. These results shed some light on the microglial changes that might occur in humans post-injury and suggest that early pharmacological treatment might be beneficial. More specifically, an agent such as methotrexate might offer a sparing effect on the neurobiological changes that might otherwise subject patients to a lifelong battle with neuropathic pain.

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An update on the treatment of postherpetic neuralgia.

Wu CL, Raja SN.
J Pain 2008;**9**:S19–30.

In this article, the authors review the current analgesic options for the treatment of postherpetic neuralgia. Although the data on most therapies were somewhat equivocal, there was significant evidence for the efficacy of tricyclic antidepressants, membrane stabilizers, opioids, and lidocaine patch for this indication.

Postherpetic neuralgia (PHN), a complication of herpes zoster virus, can be extremely painful and severely debilitating. Although PHN tends to be a self-limiting condition, it can persist indefinitely and treatment is focused on analgesia while the condition resolves. PHN can be resistant to therapy, but recent studies have found evidence for the efficacy of a number of analgesic interventions. In the present study, the

authors reviewed the evidence for the efficacy of various pharmacological and interventional therapies for PHN.

The pharmacological agents reviewed included tricyclic antidepressants, antiepileptic drugs, tramadol, and opioids, and the authors also examined topical agents, psychological interventions, nerve blocks, spinal cord stimulation, and surgical options. Overall, evidence from randomized controlled trials demonstrated that tricyclic antidepressants, opioids, antiepileptic drugs, and lidocaine patches were associated with significant pain relief in patients with PHN. However, no therapy resulted in sufficient pain control in all patients, and a number of patients found that adverse medication effects outweighed the benefits. There was evidence for the efficacy of intrathecal methylprednisolone and of spinal cord stimulation, but this was limited and preliminary; therefore, further study of these interventions is needed.

In conclusion, although PHN remains a difficult condition to treat, the clinical picture appears to be more hopeful than was previously supposed. This study demonstrates that there are a number of analgesic options for the clinician and patient to choose from.

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Fentanyl-induced neurotoxicity and paradoxic pain

Okon TR, George ML.
J Pain Symptom Manage 2008;**35**:327–33.

The present authors report the case of a 76-year-old woman with metastatic cancer who developed severe neurotoxicity, including opioid-induced hyperalgesia (OIH), following fentanyl treatment for severe pain upon discontinuation of intravenous morphine. The symptoms completely resolved with discontinuation of fentanyl. This case report demonstrates that OIH can occur in the context of standard management of cancer pain, and can be successfully treated by opioid reduction and rotation.

The patient described in this case report suffered from metastatic leiomyosarcoma, which had extensively involved the pelvis, sacral plexus, and sciatic nerve. Severe, mixed, neuropathic-nocioceptive pain was treated using a fentanyl patch, for which doses were rapidly increased during an episode of fever and sepsis. After naloxone was administered for severe sedation and the dose of the fentanyl patch was reduced, the patient was transferred to a palliative care facility for pain control. After changing to moderate dose, intravenous basal and demand fentanyl therapy, cutaneous hyperalgesia was noted with sensorium changes. As a result of persistent, severe pain, larger intravenous boluses of fentanyl were administered resulting in moderate somnolence and apparent comfort. The basal and bolus doses of fentanyl were then increased to 60 μg/h and 40 μg every 10 min, respectively. Recurrent hallucinations were noted with objective myoclonus, which resolved upon discontinuation of the fentanyl infusion.

This case is discussed primarily to illustrate the importance of recognizing opioid-induced hyperalgesia (OIH), also known as paradoxical pain, as well as the better recognized nonspecific opioid neurotoxicities. While the authors know of no prior reports of OIH on relatively low-dose intravenous fentanyl, they point out the probable contribution of drug accumulation from earlier dosing. This is exacerbated by the long elimination half-life, stated as being in excess of 200 min.

The authors discuss in detail the possible mechanisms involved in the development of OIH. In particular, OIH can occur in the following circumstances:

- During opioid maintenance and withdrawal.
- During dose escalation.
- With ultra-high doses, especially with phenantrene opioids (e.g. morphine).
- With ultra-low doses.

Mechanisms for OIH are postulated. These include antagonist or agonist action on different opioid receptors, or facilitation of transmitter release directly from the brainstem combined with the influence of genetic factors. Specifically, the potential role of *N*-methyl-D-aspartic acid (NMDA) receptors in OIH is given considerable attention. Studies have shown that activation/inhibition of NMDA receptors can impact opioid responsiveness and influence neuroexcitation in spinal neurons. This correlates with data from animal studies showing sustained hyperalgesia with increasing fentanyl administration. The potential role for the blockade of NMDA receptors in OIH is discussed.

This case offers a significant contribution to the literature on OIH, with hyperalgesia and other neurotoxicities developing during what may be regarded as standard management of severe cancer pain. It needs to be re-emphasized that the transdermal fentanyl patch creates a reservoir of medication beneath the skin. Absorption into the bloodstream from this depot may not reach full concentration for 24 h, with approximately 50% of the drug still present in the depot 24 h after removal of the patch. Perhaps most importantly in this case, delivery of fentanyl to the skin reservoir is increased by fever, which can boost absorption into the blood by >30%.

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BREAKTHROUGH PAIN

Bioequivalence following buccal and sublingual placement of fentanyl buccal tablet 400 μg in healthy subjects

Darwish M, Kirby M, Jiang JG et al.
Clin Drug Investig 2008;**28**:1–7.

The study assessed the bioequivalence of a single 400-μg dose of fentanyl buccal tablet (FBT) following buccal and sublingual placement in order to provide an alternative option to patients using FBT for the management of breakthrough pain. The study consisted of 90 subjects. The results showed that the criteria for bioequivalence for sublingual compared with buccal placement of FBT had been met, indicating that sublingual placement is a reasonable alternative for opioid-tolerant patients requiring treatment with FBT.

Originally developed for buccal administration, fentanyl buccal tablet (FBT) may also be placed – due to need or preference – in the sublingual area so as to take advantage of greater salivary flow. The current investigators realized that in order to provide alternative placement options to patients requiring FBT, it was necessary to examine variations in the pharmacokinetic profiles of buccal compared with sublingual FBT placement. Therefore, the objective of this study was to assess the bioequivalence of buccal and sublingual placement in healthy opioid-naïve subjects after a single dose of FBT 400 μg.

Bioequivalence was determined from maximum plasma drug concentration (C_{max}) and area under the plasma drug concentration–time curve (AUC) measurements, and would only be established if the 90% confidence interval for the ratio of the means of sublingual/buccal values fell within the range of 0.80–1.25.

A total of 90 subjects were randomized to one of two open-label, single-dose sequences (buccal then sublingual or sublingual then buccal placement). The interval between each FBT placement was at least 7 days. A supplementary 50-mg tablet of naltrexone was given to each subject approximately 3 and 15 h before and 9 h after each FBT administration, with the purpose of blocking opioid receptors and minimizing opioid-related effects. A placebo tablet matching FBT was administered the night before FBT placement in order to familiarize subjects with the correct usage of the study tablet.

The AUC and C_{max} values were found to be similar for buccal and sublingual placement of FBT and the predefined criteria for bioequivalence were met. FBT was well tolerated following both buccal and sublingual placement. Thus, the authors concluded that sublingual FBT placement is a reasonable alternative for patients receiving buccal FBT treatment.

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Opioids for cancer breakthrough pain: a pilot study reporting patient assessment of time to meaningful pain relief

Zeppetella G.
J Pain Symptom Manage 2008;**35**:563–7.

This small, open-label study describes the characteristics of breakthrough pain and time to analgesia following administration of rescue medications in hospice patients. The results showed that oral transmucosal fentanyl citrate was significantly more effective in producing analgesia and had a more rapid onset compared with morphine, oxycodone, hydromorphone, and methadone.

Breakthrough pain (BTP) is a transient increase in moderate or severe pain intensity, occurring in the presence of well-established baseline pain. A seminal study by Portenoy and Hagen characterized BTP as rapid in onset (within 3 min) and short in duration (median 30 min) [1].

To manage BTP, normal-release opioids, known as rescue medications (RMs), are used (e.g. morphine, hydromorphone, and oxycodone) although oral formulations of these opioids may delay the onset of analgesia (up to 60 min). In contrast, rapid-onset opioid formulations, including oral transmucosal fentanyl citrate (OTFC), have a rapid absorption and therapeutic effect (15 min). This study's goals were to characterize BTP in a sample of hospice inpatients (n=50) and to determine the time to analgesia following administration of different RMs.

Patients were asked to describe BTP characteristics, and then used a stopwatch to record the time between the use of RMs and the onset of analgesia. Five BTPs were recorded per patient.

Descriptive analyses showed that most of the sample included lung, breast, and prostate cancer patients (mean age 68 years, range 32–88 years). Around the clock (ATC) medication dosages were relatively comparable in potency.

Patients reported a mean of 1.7 (range 1–4) different types of BTP, with a mean duration of 35.2 min (range 15–60 min), with no significant differences between drug groups. The mean number of daily BTP episodes was four (range 1–8), of which:

- 68% occurred spontaneously.
- 57% were severe.
- 59% were unpredictable.

The results of RM effectiveness indicated that OTFC was significantly more effective compared with oral opioids (all p values <0.05), with no differences among oral opioids. The mean time to onset of analgesia was 31 min (range 5–75 min). Morphine, oxycodone, and hydromorphone had no difference in relative potency; methadone was significantly quicker than morphine, but not than oxycodone or hydromorphone, and OTFC was significantly quicker than all other drug groups (all p values <0.05).

The strengths of this study include comprehensive information on BTP, novel data on time to analgesia, topical significance, and real-time data on analgesia onset. The study would have benefited from a randomized double-blind design, a larger sample size, and a titration period for oral opioids.

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The Alberta breakthrough pain assessment tool for cancer patients: a validation study using a Delphi process and patient think-aloud interviews

Hagen NA, Stiles C, Nekolaichuk C et al.
J Pain Symptom Manage 2008;**35**:136–52.

This study describes the development and initial validation of a new assessment tool for the measurement of breakthrough pain (BTP) using a rigorous methodology. Expert review showed a high level of agreement with item content. Cancer patients confirmed comprehension of items. Preliminary results established that the tool has good construct validity and content validity. Further validation of this innovative tool is warranted, and its potential use in clinical trials for BTP appears promising.

Rates of breakthrough pain (BTP) are high in cancer patients (40–93%). BTP is associated with high levels of psychological distress, decrements in quality of life, and greater healthcare costs. Despite these effects, no validated measurement instrument for the evaluation of BTP has been published to date. Therefore, the main goal of this study was to develop and preliminarily validate a measurement tool for BTP to use in clinical research trials.

Measure development in the study included four primary steps:

1. A national panel of 16 pain experts in Canada developed a series of items to assess BTP, including BTP characteristics, temporal dynamics, patient satisfaction with management, and potential etiology. A total of 18 items were generated that addressed important BTP outcome areas for research interventions.
2. Items were administered to cancer patients with BTP (n=5) who further refined them.
3. A Delphi process was used to further establish expert consensus on the items. An international expert panel (n=22) and the Canadian national panel completed anonymous surveys on the following domains: item adequacy, clarity, response format, and response options. Mean agreement across domains was 80% for the national panel and 88% for the international panel. Total return rates for the surveys were 56% for the national panel and 73% for the international panel.
4. Items were finalized using a comprehensive structured clinical interview ("think-aloud" interviews) with cancer patients (n=9) in a tertiary hospital. The interview integrated recommendations from the panels. Interviews were transcribed and coded by two independent raters.

This study used the Delphi process and patient think-aloud interviews to design a clinician-administered tool for the measurement of BTP. The preliminary results showed that the tool had good content and construct validity. Based on these findings, additional research on the psychometric properties of the tool is needed, including construct validity, criterion validity, and reliability.

The novel application of the Delphi process to develop a BTP tool, the methodological approach that included patient think-aloud interviews to pretest tool items, and the development of one of the first known measurement tools for BTP make this a particularly interesting study.

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OPIOIDS

Opioid use in palliative care of children and young people with cancer

Hewitt M, Goldman A, Collins GS et al.
J Pediatr 2008;**152**:39–44.

This aim of this prospective, multicenter survey was to identify the opioids prescribed, the preferred routes of administration, and the specified dosages in children and young adults (aged 0–19 years old) with cancer in the UK. Of 185 participants, 89.6% received major opioids. Median monthly maximum doses increased from 2.1 mg/kg/day at the beginning of the study to 4.4 mg/kg/day at the very end of life.

The format of this survey was monthly questionnaires for 6 months or until death. A total of 22 oncology centers participated and 185 patients were enrolled, of whom, 164 died during the study.

The results showed that the mean duration of palliative care was 67 days. Overall, 89.6% patients were taking major opioids, and 44.5% received more than one major opioid. The most frequent combination of major opioids was morphine–diamorphine (62 patients) and morphine–fentanyl (14 patients). Those patients who did not receive any major opioid during palliative care (17 patients) were prescribed non-opioid analgesics (13 patients), minor opioids (six patients), or no analgesic medication (four patients).

The most frequent route of administration of major opioids was oral (71.3% of patients). Other routes used were intravenous (41.5%), subcutaneous (28%), rectal (12.2%), and transdermal (only fentanyl; 11%). In the more terminal periods of life, there was a change in the route of administration – the most frequent was intravenous (33%), followed by oral (26%) and subcutaneous (23%). The median monthly maximum doses of opioid increased from 2.1 mg/kg/day at the beginning of the study to 4.4 mg/kg/day at death.

This study provided baseline data for pediatric palliative care practice and is relevant for evolving evidence-based approaches to the practice of palliative medicine in children.

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Trends in opioid prescribing by race/ethnicity for patients seeking care in US emergency departments

Pletcher MJ, Kertesz SG, Kohn MA et al.
JAMA 2008;**299**:70–8.

The present authors determined whether rates of opioid prescribing for patients seeking pain treatment in US emergency departments were associated with patient racial/ethnic status. The results showed that white patients were significantly more likely to receive prescriptions for opioids compared with non-white patients, despite pain type or severity. These findings suggest that racial/ethnic minority patients treated in emergency departments are at higher risk of inadequate pain treatment compared with white patients.

Patients from racial/ethnic minorities are more likely than non-minority patients to have their pain symptoms underestimated and undertreated in the US. Emergency departments (EDs) are frequently utilized for pain care and are ideal settings for evaluating the relationship between opioid prescribing and race/ethnicity. Using national survey data, this study evaluated whether there were disparate rates of opioid prescribing in EDs by race/ethnicity.

The number of pain-related visits to US EDs between 1993 and 2005 was analyzed using National Hospital Ambulatory Medical Care Survey data. The primary complaints or reasons for ED visitation were recorded. Any complaint noted as pain-related or injury-related was analyzed. The primary outcome was whether any opioid analgesic was prescribed for the complaint. Independent variables included race (white, black, Asian/Pacific Islander, Native American, other, and multiple) and ethnicity (Hispanic or non-Hispanic). Potential covariates included age, sex, insurance, substance or alcohol abuse disorders, and hospital region, owner, and setting.

The results showed that between 1993 and 2005, 374 891 US ED visits occurred. Of these, 42% were pain-related visits (race/ethnicity: white 66%; black 20%; Hispanic 11%, and Asian/other 2%). Compared with white patients, black patients were younger, less likely to have health insurance, and more likely to have sickle cell disease. Between 1993 and 2005, opioids were prescribed in 29% of pain-related visits, with rates increasing over time (23% in 1993 vs. 37% in 2005). Over the 13 years of the study, opioid prescribing rates were highest among white patients (31%) and lowest among black patients (23%). Prescribing rates for Hispanic and Asian/other patients were 24% and 28%, respectively. In 2005, group differences persisted with opioids prescribed in 40% of white patients versus 32% of non-white patients.

The effects of pain type, pain severity, visitation reason, and diagnosis of long-bone fracture or nephrolithiasis did not attenuate the disparities. As pain severity increased, group differences widened, especially for back pain, headache, abdominal pain, and other pain. Black patients, especially children, were significantly less likely to receive opioid prescriptions compared with any other group. Hispanic children, black patients who self-paid and were treated in government-owned (non-federal) hospitals, Asians/others with Medicare, and non-whites in Northeast hospitals were less likely to receive opioids. Differential rates were due to lower rates of prescription of hydrocodone, Schedule II opioids, and all opioids except codeine. Non-white patients were more likely than white patients to receive non-opioid analgesics (26% vs. 32%).

Despite national increases in the rate of opioid prescription in EDs between 1993 and 2005, racial/ethnic minority patients treated for pain in EDs were less likely to receive opioid prescriptions; furthermore, these racial/ethnic disparities were stable over a 13-year period.

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MISCELLANEOUS

The role of catastrophizing in sickle cell disease – the PiSCES project

Citero Vde A, Levenson JL, McClish DK et al.
Pain 2007;**133**:39–46.

Catastrophizing is well-known to contribute to pain intensity and disability in chronic pain populations. This study evaluated the role of catastrophizing in patients with sickle cell disease (SCD) and its impact on psychosocial well-being, pain, and healthcare utilization. SCD patients had higher levels of catastrophizing compared with other chronic pain populations, with mixed results for the effects of catastrophizing on pain outcomes. The findings show that catastrophizing has a differential magnitude and impact in SCD patients versus other chronic pain populations.

Catastrophizing is a maladaptive coping strategy that includes magnification, rumination, and helplessness. It leads to increased pain behavior, health service usage, and hospital stays [1]. Patients who catastrophize report more intense pain, psychological distress, and disability compared with patients who do not catastrophize [2]. To date, few studies have evaluated the nature and impact of catastrophization on pain outcomes in patients with sickle cell disease (SCD). The primary aim of this study was to evaluate the effects of catastrophization on psychosocial well-being, pain, and healthcare utilization in 220 SCD patients.

SCD patients enrolled in an epidemiological cohort study completed daily pain diaries for up to 188 days (or 6 months). Baseline and 6-month follow-up data were collected. Primary outcomes included:

- Pain responses (pain intensity, pain-related distress, and pain-related interference).
- Crisis and non-crisis SCD-related pain (including health service usage and type).
- Quality of life (QoL).
- Depression.

Participants were trained to complete and postmark daily pain diary data to reduce measurement error and non-adherence. It was hypothesized that higher levels of catastrophization would be associated with significantly higher levels of pain intensity, pain-related distress, pain-related interference, and health service usage versus lower levels of catastrophization.

Multivariate analyses, controlling for depression, showed that catastrophization did not predict pain responses, and neither did it predict crisis or non-crisis SCD-related pain, including health service usage. Additional findings demonstrated the following:

- Higher levels of catastrophization were associated with poorer a QoL across all domains (all p values <0.001).
- There was a strong positive correlation between depressive symptoms and catastrophization (r=0.48; p<0.001).
- Catastrophization was significantly higher among SCD patients with the less severe SCD genotype when controlling for the effects of depression, age, gender, and marital status (p<0.001).
- Catastrophization was not significantly related to age or education.

These findings are significant in several regards. The severity of catastrophization in SCD patients was higher than in other chronic pain studies. Contrary to the study hypotheses, high and low catastrophizers did not vary according to pain responses or to crisis or non-crisis SCD-related pain (when controlling for the effects of depression). Unexpectedly, catastrophization was greater in patients with the less severe SCD genotype. Thus, this well-designed study suggests that the role of catastrophizing may be quantitatively different in SCD patients than other chronic pain populations. These data may have encouraging implications for identifying the factors affecting pain experience in this understudied population.

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Perineural injection of etanercept as a treatment for postamputation pain

Dahl E, Cohen SP.
Clin J Pain 2008;**24**:172–5.

Systematic treatment with drugs that block the inflammatory cytokine tumor necrosis factor α (TNF-α) has been shown to alleviate neuropathic pain. However, little is known about efficacy of local administration of these drugs. The study reports results on use of perineural etanercept in six patients with postamputation pain. In five of six patients, perineural application of etanercept resulted in significant pain relief.

The inflammatory cytokine tumor necrosis factor α (TNF-α) is a key factor in the development and maintenance of chronic pain conditions. Systemic treatment with drugs that inhibit TNF-α has been shown to alleviate neuropathic pain. Similar to other classes of drugs used to treat neuropathic pain, TNF inhibitors exert their analgesic effect via both local and systemic mechanisms. Although both means of administration produce pain relief, findings from a recent preclinical study suggests that benefits from perineural injection may be more profound and enduring [1].

The authors of this study investigated the effects of perineural etanercept (a TNF inhibitor) in patients with post-amputation pain. They present a series of six cases, comprising traumatic amputees with residual limb pain and phantom limb pain who were treated with a set of locally administered perineural injections of etanercept. Each injection consisted of etanercept 5 mg in 5 mL of water. The treatment regimens varied in each of the six patients with regard to the number and frequency of injections administered.

The initial pain intensity in five of the six patients was moderate-to-severe (limb pain scores of 7–10 out of 10), amputee number 6 reported mild-to-moderate pain (limb pain scores of 2–5 out of 10). At the follow-up 3 months after treatment, significant pain relief was noticed in five cases; one patient reported only a minimal reduction of pain. No adverse events were observed.

These findings demonstrate that TNF-α inhibitors can be efficacious in patients with post-amputation neuropathic pain. Moreover, the local application of etanercept seems to be safe, as no side effects were experienced. As the authors noted, this is the first clinical study to provide evidence of sustained pain relief following local application of a TNF inhibitor.

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Clinical findings in men with chronic pain after falanga torture

Prip K, Persson AL.

Clin J Pain 2008;**24**:135–41.

These authors investigated the clinical characteristics of chronic pain in victims of falanga years after their experience, with the aim of delineating the mechanism of pain. They compared feet and lower leg symptoms of 11 torture victims with 11 matched controls. All victims had pain in their feet and lower legs that usually increased with walking. Two types of neuropathic pain were evident.

In 106 of 161 countries torture is still sanctioned by their governments. The most frequently used method is beating of the victim's body with a blunt instrument. The repeated beating of the soles of the feet with a blunt object is a relatively common form of torture and known as falanga. In addition to severe pain, immediate effects are bleeding and edema of the feet and swelling of the lower legs. Years later, chronic pain is often still experienced by falanga victims in the feet and lower legs. The present authors, from the Rehabilitation and Research Centre for Torture Victims in Copenhagen, Denmark, examined this chronic pain experienced by falanga victims, with the aim of understanding the mechanisms behind it.

The study group comprised 11 male falanga victims (eight from Iraq and three from Iran) who were compared with age-, sex- and ethnicity-matched control subjects. These controls were first-generation immigrants from Arabic countries living in Copenhagen. The average age of the torture victims and controls was 42.5 and 39.3 years, respectively. Time since exposure to torture was >5 years.

All torture victims described pain in their feet and lower legs while walking. Such pain was also experienced by four control subjects; however, in these individuals this could be accounted for by structural anomalies such as hallux valgus or heel spur, or a job that required standing for long periods of time. In addition, 10 of the falanga victims had an abnormal gait with abnormal toe-off and a phase off over the lateral borders of the feet, interpreted as a compensatory strategy to decrease pain induced by weight-bearing.

Sensory disturbances were not seen in the control subjects, but 12 of the victims' feet displayed a reduced sense of light touch, 11 showed reduced thermal sensation, 20 had areas of tactile dysesthesia, and five had signs of allodynia. Nine of the victims had reduced heel elasticity and seven had flat wide heel pads in comparison with the controls, which has been reported to be associated with plantar heel pain. However, the authors caution that as this was assessed by palpation, this measure may be subject to bias.

From these results the authors proposed that pain experienced by their group of falanga victims could be divided into two types. "Stimulus-evoked pain" increased in severity with walking while "symptom-independent pain" did not. As most feet in which the latter type of pain was experienced had impaired sensory function in both large and thin afferent fibers, the authors suggest that this pain could potentially be explained by spontaneous activity evoked in C-fibers and group IV afferents caused by mechanical injury of the nerve bundles in the soles of the feet. However, feet with stimulus-evoked pain were more prone to sensory symptoms such as dysesthesia and allodynia and, therefore,

the mechanism of this pain is more likely to be related to central sensitization.

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The relationship between clinical parameters and depression level in patients with myofascial pain syndrome

Altindag O, Gur A, Altindag A.
Pain Med 2008;**9**:161–5.

Major depressive disorder (MDD) in patients with myofascial pain syndrome (MPS) has not been well-described to date. This study identified the prevalence, characteristics, and correlates of MDD in patients diagnosed with MPS. The results showed that MPS patients had significantly higher rates and severity of MDD compared with non-pain controls, with a strong and significant positive correlation observed between pain intensity and depressive severity. The findings suggest that the rates of MDD are comparable to those found in other chronic pain subpopulations.

Rates of major depressive disorder (MDD) are high among chronic pain populations. Few studies have focused on MDD in patients with myofascial pain syndrome (MPS). Only four published studies have evaluated depression in MPS populations [1–4], with only one known study including a control group [4].

The primary aim of this study was to identify the prevalence, characteristics, and correlates of MDD in patients with MPS in Turkey. To accomplish this aim, two groups were compared: group 1 consisted of adults diagnosed with MPS (n=77) and group 2 adults without chronic pain (n=72; comprised of family members of MPS patients in group 1).

Participants completed a battery of self-report measures assessing pain characteristics and pain-related disability. The presence of MDD was diagnosed by a psychiatrist based on the Diagnostic and Statistical Manual of Mental Disorders (4th edition) criteria. To establish depression severity, the Beck Depression Inventory (BDI) was administered (only the cognitive–affective subscale was used to control for the confounding effects of somatic items).

MDD prevalence was higher in MPS patients (39%) compared with non-pain controls (4%). Consistent with this finding, mean BDI scores were significantly higher in MPS patients compared with non-pain controls.

A strong and significant positive correlation was observed between the BDI and pain intensity scores ($r=0.65$; $p<0.001$). As expected, mean pain and pain-related disability levels were higher in MPS patients compared with non-pain controls.

These findings suggest that MDD rates among MPS patients (39%) are comparable to those of other chronic pain populations (range 30–54%). Consistent with previous research, MDD and pain intensity were positively correlated.

The strengths of this study include its rationale, well-defined inclusion and exclusion criteria, detailed recruitment statistics, inclusion of a non-pain control group, and comparison of depression rates with those of other published studies. This study could have been strengthened by the use of a non-random sample, inclusion of a control group that did not include family members of patients with chronic pain (rates of psychological distress are often elevated in family members of chronic pain patients, although not in this study), and use of multiple raters for MDD to establish inter-rater reliability.

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Patients' self-criticism is a stronger predictor of physician's evaluation of prognosis than pain diagnosis or severity in chronic pain patients

Rudich Z, Lerman SF, Gurevich B et al.
J Pain 2008;**9**:210–6.

Few studies have identified factors that influence physicians' formulations of pain prognosis in chronic pain treatment. This study evaluated whether patients' personality characteristics influenced physicians' formulations of pain prognosis. The results showed that higher levels of self-criticism in chronic pain patients was the most important predictor of physician pessimism about the expected impact of pain treatment. These findings may warrant future research on the effects of self-criticism on physician attitudes and perceptions.

Psychological factors are known to influence pain outcomes. Accordingly, psychological factors may drive physician formulations of pain prognosis with chronic pain treatment. One psychological factor that may impact physicians' evaluations of pain prognosis is patient self-critcism – a personality trait characterized by perfectionism and

psychological distress, and may lead to negative interpersonal relationships. In this study, self-criticism was hypothesized to negatively impact the physician–patient relationship.

The investigators aimed to evaluate the relationship between self-criticism in chronic pain patients and physician formulations of expected prognosis. To accomplish this aim, 64 patients with various chronic pain syndromes completed a battery of self-report measures that assessed self-criticism, depression, and pain characteristics. Following battery completion, three pain specialists blind to the self-report scores completed a two-item rating scale evaluating pain prognosis.

Simple correlation coefficients showed that self-criticism was significantly and positively associated with physician pessimism regarding pain prognosis ($r=-0.36$; $p<0.001$). Additionally, pain level was significantly and positively associated with physician pessimism regarding pain prognosis ($r=-0.24$; $p<0.05$). Relationships between pain prognosis and other variables were not statistically significant.

Standard multiple regression analyses showed that self-criticism was an independent predictor of physician pessimism regarding pain prognosis when controlling for pain level and depression ($R^2=0.13$). Subsequent regression analyses demonstrated that self-criticism was an independent predictor of physician pessimism concerning pain prognosis when controlling for pain diagnosis, physician, pain duration, and patient age and gender.

Self-criticism in chronic pain patients appears to be a robust predictor of physician pessimism regarding pain prognosis. The researchers conclude that self-criticism has a demoralizing effect on physicians' clinical judgment; however, this was not directly evaluated in the study. They posit that self-criticism potentially drives patient dissatisfaction with pain treatment and negative expectations about treatment efficacy.

The study strengths include the methodological rigor, the use of standardized instruments to measure depression and pain, and the novel area of research. This study would have benefited from the development and evaluation of an explanatory model for understanding the relationship between self-criticism and pain prognosis. Furthermore, the investigators did not examine the mechanisms that potentially mediate or moderate the association between self-criticism and pain prognosis. Despite the study implications, physician demoralization and its effects on clinical judgment were not directly evaluated. Future studies could address these issues and patient–physician communication to determine the role of self-criticism on the formulation of pain prognosis.

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Chiropractic: a critical evaluation

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J Pain Symptom Manage 2008;**35**:544–62.

This review describes the benefits and risks of chiropractic techniques used for the treatment of chronic pain. Studies show that chiropractic techniques may demonstrate a mild benefit in relieving back pain; however, none can be recommended due to the lack of quality randomized controlled trials to date.

In the US, 3–18% of the general population uses chiropractic techniques for the treatment of chronic pain and this proportion is growing. There is little information on the potential benefits of chiropractic techniques for relieving chronic pain to date. Therefore, the present authors conducted this literature review to describe the effects of chiropractic techniques on chronic pain in the context of historical conflict and controversies within the profession.

History: DD Palmer is widely credited with establishing chiropractic medicine in 1895. The premise of chiropractic medicine is based on the notion of "innate intelligence", which Palmer coined as an immeasurable life force that is present within all humans and essential for bodily health and healing. Pain is viewed as a disruption in innate intelligence and is due to subluxation. Controversy exists between those in the profession who base their practice on theories of empiricism and those who favor evidence-based medicine. Many chiropractors believe that subluxation is the primary cause of numerous diseases, including chronic pain disorders. They assume that subluxation is caused by misaligned vertebra and can be fixed by spinal manipulation using chiropractic techniques. Multiple theories have been proposed for the etiology of subluxation, with no scientific evidence to support these explanations to date.

Treatment: Multiple techniques are used in combination with spinal manipulation, including thermal, cold, electrotherapy, lifestyle modification, homeopathy, and kinesiology. Many patients are self-payers for chiropractic services, though Medicare does cover services. Indications for chiropractic therapies mainly include back pain (60% of all patients who seek services [1]), neck pain, and other musculoskeletal conditions; however, they are used for numerous diseases. Multiple diagnostic tests are used, especially radiographic investigations, with limited validity and reliability.

Effectiveness: Current evidence from systematic reviews shows that randomized controlled trials for spinal manipulation have no significant benefits except for back pain. Spinal manipulation may be equally as effective as standard care for back pain, particularly for selected subpopulations. Most

studies have lacked control conditions, and there is potential publication bias in the literature.

Safety: Despite claims from the clinical literature that chiropractic therapy is safe for the majority of patients, there are compelling data to demonstrate a strong relationship between chiropractic techniques and a high rate of adverse effects.

Cost: Chiropractic techniques have not been shown to be cost-effective compared with traditional therapies, including treatment by primary care physicians.

Studies show that chiropractic techniques may demonstrate only a mild benefit in relieving back pain, with none that can be recommended due to the lack of quality randomized controlled trials to date. The popularity of chiropractic techniques continues to grow worldwide despite insufficient evidence for their efficacy.

1. Carey TS, Evans AT, Halder NM et al. Acute severe low back pain. A population based study of prevalence and care seeking. *Spine* 1996;**21**:339–44.

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Clinical and economic impact of palliative care consultation

Hanson LC, Usher B, Spragens L et al.
J Pain Symptom Manage 2008;**35**:340–6.

Using a controlled design, this prospective observational study evaluated the effects of palliative care consultations on symptoms and end-of-life treatments in hospitalized patients. The findings showed that inpatients referred for palliative care consultation demonstrated statistically significant reductions in symptom severity; these consultations were not associated with higher costs, but in fact led to significantly lower daily variable costs.

As models of palliative care consultation are introduced into clinical practice, there is a need to empirically evaluate their efficacy and cost effectiveness. The primary objective of this descriptive study was to determine the effects of palliative care consultation on symptoms and treatments, and the extent to which palliative care consultation decreased hospital-related costs.

Between 2002 and 2005, the palliative care consultation team in a large tertiary care hospital treated 395 patients, 304 of whom participated in this study. Patients were referred to a multidisciplinary team trained in palliative care for a variety of physical and psychosocial symptoms. Demographic characteristics, primary illness, reason for referral, consultation results, pre-consultation performance status, and symptom characteristics were assessed. Symptoms were evaluated prior to, and during the intervention using either a daily self-report measure or a clinician rating scale. To examine the role of palliative care consultations on hospital-related costs, a large database of matched controls (n=1813) was used as a comparison group for a subsample of 104 study patients (All Patient Refined Diagnosis Related Group, 3M Version 20).

Sample characteristics showed that median age was 66 years, 58% were women, 28% were African American, 61% had cancer as their primary illness, and the median Palliative Performance Scale score was 20. The top three reasons for referral were to provide aid with end-of-life decision-making (88%), pain (57%), and dyspnea (45%). At day 3 of symptom monitoring, pain, dyspnea, and nausea showed statistically significant reductions using paired *t*-tests (all p values <0.05).

The treatments recommended by the consultation team were employed in 88% of patients, with 26% receiving new "do not resuscitate/do not intubate" orders and 34% receiving a new comprehensive palliative care protocol order.

In patients whose length of stay was >4 days, cost analyses showed that palliative care consultation was associated with significantly lower daily hospital costs (US$897) compared with matched controls who were not referred but had similar mortality risk and illness severity (US$1004; p<0.03). Within-group analyses showed that patients who had palliative care consultations on more than 50% of their hospitalization days had significantly lower costs (20.5%) than the entire sample who had palliative care consultations on more than 25% of their hospitalization days. Thus, longer duration of palliative care intervention was associated with lower hospital-related costs.

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A scale to measure pain in non-verbally communicating older patients: the EPCA-2 Study of its psychometric properties

Morello R, Jean A, Alix A et al.
Pain 2007;**133**:87–98.

The Elderly Pain Caring Assessment 2 is an eight-item behavioral scale that was constructed to rate the intensity of pain in non-verbally communicating patients aged ≥65 years.

Pain is a complex, multifactorial phenomenon. Subjective aspects of pain include intensity, psychological consequences, and quality of life; therefore, a comprehensive analysis of the effects of pain and pain therapies should include patient self-reports. However, such evaluations can be difficult in patients

who are unable to provide reliable verbal reports (e.g. those with dementia), and researchers must rely on behavioral assessments in order to measure pain intensity in such patients.

These authors identified a lack of a properly validated clinical scale to measure pain in non-verbally communicating older patients (NVC-OPs) in the published literature, and devised the Elderly Pain Caring Assessment 2 (EPCA-2) scale in order to provide a simple tool for use in daily clinical practice. The EPCA-2 was based on signs of pain reported by 48 experienced nurses and caregivers and described in the published literature. Behaviors indicative of pain during caregiving interventions (e.g. reactions to being moved and complaints) were considered separately to those at rest, during interactions with others, and spontaneous movements.

Following tests of the psychometric properties of initial versions of the scale the EPCA-2 was refined to eight items, each of which was graded on a five-point scale of 0–4 (no pain to extremely intense pain). Four items on the scale applied to signs of pain observed during the 5 min prior to caregiving:

- Facial expression.
- Spontaneous posture adopted at rest (trying to find a comfortable position).
- Movements of the patient out of bed and/or in bed.
- Interaction of all kinds with other people.

The authors recommended that signs of pain during caregiving should be recorded and graded immediately after the intervention, and should report on the following four items:

- Anxious anticipation of caregiver intervention.
- Reactions during caregiver intervention.
- Reactions of the patient when painful parts of the body are nursed.
- Complaints voiced in the course of caregiving.

Mean observation times for reliable assessment were calculated to be 4.8 min and 5.2 min for before and during caregiver intervention items, respectively. Tests of the validity of the psychometric properties of the final version included a study of 340 NVC-OPs. The EPCA-2 correlated well with a pain global clinical score and opioid dose administered to a subgroup of 112 patients (Spearman's correlation coefficient scores of 0.8456 and 0.698, respectively). The inter-rater reliability of the scale was reported to be very good, and was consistent for doctors, nurses, and caregivers, and the internal consistency was deemed to be highly satisfactory.

The authors recommend that, following a short training period, the EPCA-2 may help doctors, nurses, and caregivers to evaluate pain intensity in NVC-OPs. However, in order for this scale to yield reliable assessments of the levels of pain experienced, the care provider must be familiar with the patient and their behavior.

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MEETING REPORT

Highlights From the American Academy of Pain Medicine 24th Annual Meeting

Orlando, FL, USA, February 12–16, 2008

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The American Academy of Pain Medicine (AAPM) annual meeting 2008 was a highly informative meeting that updated attendees from around the world on the growing field of pain medicine. The meeting provided useful tools for comprehensive evaluation and treatment of the pain patient. The majority of attendees were pain specialist physicians from a variety of disciplines including anesthesiology, neurology, neurosurgery, physical medicine and rehabilitation, family medicine, primary care, and psychiatry from both the academic as well as private practice area. The meeting included keynote and plenary lecturers, scientific presentations, and refresher sessions in addition to the pain medicine review course.

New concepts and knowledge in pain medicine

A statement from the American Pain Society and AAPM states that the undertreatment of pain is unjustified. Pain management is a fundamental human right in all patients not only with acute postoperative pain but also in patients suffering from chronic pain. Treating the underlying cause of pain does not usually treat all of the ongoing pain. Minimal pathology with maximum dysfunction remains the enigma of chronic pain. Chronic pain is only recently being explored as a complex condition that requires individual treatment and a multidisciplinary approach. It is considered to be a disease entity. The recognition of peripheral sensitization in addition to central sensitization and the identification of a large number of neurotransmitters (tissue growth factors and neuropeptides that play a major role in the peripheral mechanisms that influence nociception) provide an understanding of the mechanisms of chronic pain conditions.

The role of genetics in chronic pain will play a significant role in the therapy of chronic pain. Gain-of-function mutations or dysregulated expression of voltage-gated sodium channels can produce neuronal hyperexcitability, leading to acute or chronic pain. The sodium channel Na(v)1.7 is expressed preferentially in most slowly conducting nociceptive neurons and in sympathetic neurons. Gain-of-function mutations in the Na(v)1.7 channel lead to neuron hyperexcitability associated with severe pain, whereas loss of the Na(v)1.7 channel in patients leads to indifference to pain. The contribution of Na(v)1.7 to pain and the absence of motor and cognitive deficits in patients lacking this channel make it an attractive target for the treatment of neuropathic pain. In addition, the new knowledge about the presence of genes that control the release of nitric oxide (NO) and the role of NO in spinal hyperalgesia is likely to play a role in the treatment of neuropathic pain conditions.

Central nervous system processing

Local morphological alterations of the brain in areas related to the transmission of pain were detected in patients suffering from several pain conditions such as phantom pain, chronic back pain, irritable bowl syndrome, fibromyalgia, and chronic tension headaches. These anatomical, physiological, and chemical alterations were different for each pain syndrome but overlapped in the cingulate cortex, the orbitofrontal cortex, the insula, and dorsal pons. The question arises whether these changes, that could be secondary to frequent nociceptive input, are the cause or the consequence of chronic pain and whether these changes are reversible when the chronic pain condition improves or is adequately treated.

Opioid-induced hyperalgesia: fact or fiction?

Opioid-induced hyperalgesia (OIH) is a state of paradoxically enhanced pain sensitivity observed in both humans and animals after chronic exposure to opioids. To date, most explorations of this phenomenon's mechanism have focused on alterations in functional elements within the central nervous system and on neuroplastic changes involving primary afferent sensory neurons.

Most physicians are not aware of the OIH phenomenon. A common approach to treating increasing pain in a patient who is otherwise tolerating an opioid therapy is to escalate

the opioid dose. However, opioid therapy and titration sometimes can worsen, rather than ease, pain. Recent clinical experience and research suggests that some patients experience more pain and/or additional pain symptoms because of opioid therapy. OIH can manifest as an increased sensitivity to pain, an aggravation of pre-existing pain or the expression of novel pain symptoms.

The principal mechanisms currently considered responsible for OIH include those leading to enhanced function or activity of afferent fibers, second order or projection neurons and descending inhibitory fibers from the brainstem.

Evidence from a substantial number of animal and human studies suggest that OIH, associated with opioid maintenance therapy or withdrawal, involves the upregulation of pain facilitating neuronal pathways at multiple levels of the central and peripheral nervous system. Evidence for the existence of OIH in humans is provided by studies conducted in patients undergoing surgery, former opioid addicts maintained on methadone, study volunteers undergoing short-term infusion with highly potent opioids or acutely withdrawn from opioids, and patients suffering from chronic low back pain.

While OIH seems to be quite rare, if it is suspected dose reduction is typically associated by reduction in the hyperalgesia. Opioid rotation or complete detoxification from an opioid should be considered a management tool in this phenomenon.

Neurobiology of addiction

Drug addiction is a chronic relapsing disorder characterized by compulsive drug-seeking and drug-taking behaviors, despite negative consequences. It is described as a set of symptoms mainly involving the inability to reduce or control drug use. The National Survey on Drug Use and Health conducted by the Substance Abuse and Mental Health Services Administration estimates 22.6 million Americans aged ≥12 years, or 9.2% of the population, can be considered to have a substance abuse or dependence disorder. Moreover, one of the most significant problems for the long-term treatment of drug dependence is the high incidence of relapse to drug-seeking and drug-taking behaviors following months or even years of abstinence. To improve existing treatments, a better understanding of the neurobiological and genetic basis of addictive behavior and substance use disorder is warranted. Molecular genetic mechanism has been identified and may, in part, be responsible for the behavioral observations linking alcohol drinking and circadian rhythmicity. This mechanism involves the circadian rhythm gene. Another mechanism that could contribute to addictive behavior is a hyper-glutamatergic state, which contributes to enhanced alcohol consumption in animal studies.

Once candidate genes have been identified, characterized, and validated in humans, *in vitro* molecular biological studies can further define molecular neurobiological mechanisms mediating the genetic risk observed, which may aid in identifying potential target molecules for novel pharmaceutical therapies.

Neuromodualation and circulation

The first description of the use of electricity as a medical therapy was recorded in the year 46 BC by the Romans. During the last 10 years, the spinal cord stimulator has become a promising therapeutic option for intractable pain secondary to ischemic heart disease, peripheral vascular disease, and chronic abdominal pain secondary to chronic ischemia. Spinal cord stimulation in ischemic heart disease and peripheral vascular disease started in Europe in the 1970s and 80s. Patients with ischemic heart disease are eligible for spinal cord stimulation when they experience disabling pain resulting from ischemia that is therapeutically refractory to revascularization procedures. The absence of a prior history of heart failure and hypertension predict a favorable long-term outcome. The advantage of epidural stimulation for intractable angina-related pain is the immediate reduction of pain when stimulation is used during an attack, reduction in pain perception, reduction in sympathetic tone, reduction in the need for myocardial oxygen consumption and increased coronary microcirculation. The spinal cord stimulator also appears to be a useful treatment adjunct in end-stage, inoperable peripheral vascular disease. In peripheral vascular disease, the majority of the patients show significant reduction in pain and more than half of the patients show improvement of circulatory indices, as shown by Doppler, thermography, and oximetry studies. Limb salvage studies show variable results depending on the stage of the trophic changes. The underlying mechanisms of action of spinal cord stimulation in peripheral vascular disease require further elucidation. Spinal cord stimulation causes suppression of the sympathetic vasoconstriction allowing the microcirculation to dilate and tissue perfusion to increase. Patients need a trial period and must clearly demonstrate a positive response to the spinal cord stimulator. The endpoint is pain reduction and if not complete, almost complete, pain relief. Certainly the reperfusion index closely parallels this analgesic response; however, the patient's response is paramount. Pain could persist when the patient has developed a very deep ischemic ulcer. These ulcers are usually greater than 3 cm and cause a deep-seated and constant pain; spinal cord stimulator implantation is, therefore, not indicated.

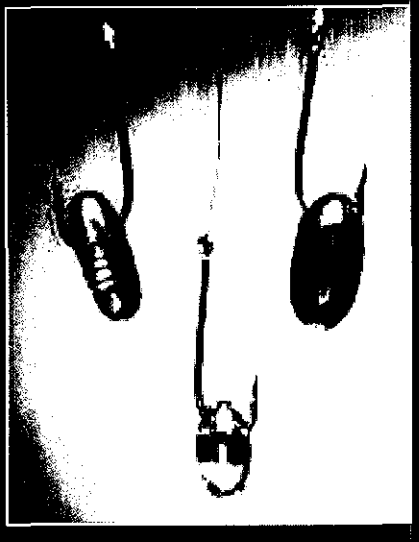
Amputation, which could be delayed by implanting a spinal cord stimulator, is strongly associated with a decrease in life expectancy and a decrease in quality of life.

Conclusion

Once again, the AAPM annual meeting proved a great success, with delegates from around the globe attending diverse and interesting sessions on a wide variety of topics in pain medicine and management. We look forward to the AAPM 25th anniversary meeting in Hawaii, USA next year.

Disclosure

The authors have no relevant financial relationships to disclose.



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