Headache
© 2016 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.12815
Published by Wiley Periodicals, Inc.

Expert Opinions

Migraine and the Risk of Suicide

Zarmeneh Aly, MBBS; Noah Rosen, MD; Randolph W. Evans, MD

Rarely and tragically, migraineurs commit suicide or overdose on medications we prescribe.

Key words: depression, migraine, suicide, overdose, comorbidity

(*Headache* 2016;56:753-761)

CASE HISTORIES

Case 1.—This 40-year-old man had an 11-year history of migraine without aura initially several times per month but daily for the last 6 years. The headaches were fairly constant of moderate to severe intensity with nausea, light and noise sensitivity, and vomiting several times monthly. Over the years, he was evaluated and treated for the headaches by a family physician, internist, allergist, ENT physician, dentist (temporomandibular joint [TMJ] specialist), an ophthalmologist, chiropractor, two pain specialists, a neurosurgeon, physiatrist, three psychologists, four neurologists, and three headache specialists. He was minimally responsive or unresponsive to all of the usual preventive and symptomatic migraine medications. Chronic opiates would dull the pain. Other treatments were not effective including two prolonged hospital stays for intravenous medications, physical therapy, TMJD treatment, three cervical epidural steroid injections for bulging discs, biofeedback, psychotherapy, a septoplasty, and allergy shots.

He was working as a business executive until 6 months previously when he went on disability. He tried to stay busy with his supportive wife and two teenage children but felt increasingly depressed despite treatment. His wife found him dead in bed with a suicide note from an overdose of opiates and antidepressants.

Case 2.—This 31-year-old woman had a history of migraine without aura since the age of 13 initially one or two times per month triggered by stress or her menses. During the prior 4 years, the headaches increased in frequency to every other day or daily with moderate to severe intensity associated with nausea and vomiting. Numerous preventive medications either were not effective or had side effects. She was tried on all of the triptans and dihydroergotamine, which were either not effective or caused side effects. She began receiving opiates from multiple primary care physicians. She had numerous visits to urgent care clinics and emergency departments for acute treatments and would often receive opiate injections. She reported some pain relief with opiates (acetaminophen combinations with codeine or oxycodone) taken alone or with oral promethazine. She also had chronic

From the Department of Neuro Oncology, Cleveland Clinic, Cleveland, OH, USA (Z. Aly); Cushing Neuroscience Institute, Hofstra Northwell Health, Great Neck, NY, USA (N. Rosen); Department of Neurology, Baylor College of Medicine, Houston, TX, USA (R.W. Evans)

Address all correspondence to N. Rosen, MD, 611 Northern Blvd, Suite 150, Great Neck, NY 11021, USA.

Accepted for publication February 26, 2016.

Conflict of Interest: None.

complaints of anxiety and depression being treated with alprazolam and paroxetine and zolpidem for insomnia. She saw several neurologists who warned her about the risks of medication rebound and discussed other treatment options.

Two weeks previously, her last neurologist advised her to taper off of opiates and referred her to a headache specialist. She reported being depressed with some suicidal ideation a couple of months previously but no specific plan. She stated that she would not hurt herself because of her three young children. Her husband, who was at the visit, was very supportive.

Two weeks later, the husband called the last neurologist saying that he found his wife dead in bed in the morning. Before going to sleep that evening, she had complained of a bad headache. Later that day, the neurologist also received a phone call from the coroner's office asking about her history. An autopsy was normal except for a drug screen which revealed high therapeutic doses of promethazine, alprazolam, zolpidem, a therapeutic dose of paroxetine, and a twice therapeutic range level of oxycodone. The forensic pathologist deemed the death an accident due to an acute combined drug intoxication.

QUESTIONS

1. Are migraineurs at an increased risk of suicide?
2. Which patients with migraine and depression require psychiatric referral?
3. If opiates are to be used in migraineurs, how might physicians protect the patients from misuse and even death and themselves from potential medical malpractice claims?
4. Tricyclics such as amitriptyline and venlafaxine are preferred migraine preventives but can also be used to overdose. Is there anything the clinician can do to prevent an overdose?
5. In case 2, how do you distinguish an overdose from a suicide?

EXPERT OPINION

Migraines are a common entity the world over with a 1-year prevalence of 11.7–13.2% in the United States. Migraine is one of the top 20 causes of disability worldwide and, only in the US and Europe, accounts for an estimated 250 million lost days from work or school every year.[1] Headaches, and particularly migraines, should be a public health priority given that they are prevalent worldwide, are usually lifelong conditions and cause disability both in terms of the disease and lifestyle restrictions they impose on the individual. Despite this, migraine is the least publicly funded of all neurological illnesses relative to its economic impact.[2] Migraine and depression are common comorbid conditions and so suicides could be extrapolated to have a high occurrence in migraineurs; however, recent literature alludes to migraines being an independent risk factor for suicides. Therefore, it is important to carefully screen such patients and identify red flags for potential referral to psychiatry. Unfortunately many of the drugs used to treat migraines carry black box warnings for suicides and some have high abuse potential, which could knowingly or unknowingly assist in suicide attempts. It is often difficult to differentiate between accidental drug overdose and suicides. This makes it all the more important for physicians to screen for comorbid psychiatric conditions and identify the risk of abuse and suicide in migraineurs.

1. Are migraineurs at an increased risk of suicide?

   Both episodic and chronic migraines have been associated with comorbid psychiatric conditions. Most recently the CaMEO study revealed that chronic migraineurs were 205% more likely to have depression and 140% more likely to have anxiety than episodic migraineurs. The presence of these psychiatric comorbidities in themselves could lead to a higher rate of suicides in migraineurs.[3] Although the bidirectional association between migraine and depression has been well documented,[4,5] awareness of the increased risk of suicide in migraineurs is a recently developing phenomenon. Ever since the first epidemiological study showing evidence of increased risk of suicide attempt among migraineurs was published in 1991,[6] there have been several studies corroborating the association.[7–11] Two large epidemiological studies have alluded

to the fact that there is a direct risk of increased suicidality associated with migraineurs, even after adjusting for the effect of co-occurring psychiatric disorders.[12,13] In a recent, large population based Canadian study, suicidal ideation was significantly more common for those with migraines.[14] However, one recent Australian population based nationwide study of chronic pain and suicide found that those with neck or back problems had the highest levels of suicidality while migraineurs were not associated with lifetime suicidality after controlling for mental health and substance abuse.[15]

Much of the research done in this area has been conducted on adolescents. The first epidemiological study showing evidence of increased risk of suicide attempt among migraineurs was published in 1991 among adolescents.[6] Ever since then, several studies, including a Taiwanese study involving 7900 students, it was found that subjects with migraines were more likely to have high suicidal risk than those without (odds ratio [OR] = 4.3).[16]

Whether this increase in the suicide risk for migraineurs is intrinsic or due to some other confounding factors is still up for debate. In December 2008, the US Food and Drug Administration issued a warning suggesting that the use of all anti-epileptic drugs (AEDs) is associated with an increased risk of suicidal ideation and behavior which is relevant since a number of AEDs are used to treat migraines.[17] Similarly, many of the antidepressants carry a black box warning since a meta-analysis of 372 randomized clinical trials showed that there was an increased rate (4 vs 2%) of suicidal thinking or behavior among patients who took antidepressants as compared with those who took placebo.[18] It is interesting to note that none of the suicide attempts documented in the trials were fatal.

2. Which patients with migraine and depression require psychiatric referral?

The data discussed prior illustrate the need for physicians dealing with migraineurs to be adept in screening for the risk of suicide. Routine screening for suicidality in migraineurs has been suggested previously; however, further research is needed before we can say that this would be effective.[14] When Sheehan et al evaluated the risk of suicides in a group of people with chronic daily headache (CDH), they found that subjects in the high suicidal risk group were more likely to be females (OR = 10.3).[16] In another population based study, although the prevalence of suicidal ideations in women was greater than that in men (10.4 vs 8.4%), this difference was not statistically significant.[14] This study also looked at the risk factor profiles of migraineurs. It showed that for female migraineurs, being unmarried, younger age, having a greater limitation in activity, and being poor were linked to suicidal ideation whereas only the first three were linked to suicidal ideations in males. White male migraineurs had a higher association with suicidality, consistent with the previously reported higher incidence in white males.[19] Classically, suicide rates are reportedly higher (by up to seven times) in those aged 75 and older than in adolescents in the general population.[20] Interestingly, in one study it was noted that migraineurs under the age of 30 had at least four times the odds of lifetime suicidal ideation than those over 65 years of age.[14] It was postulated that their increased vulnerability could be due to lack of coping mechanisms, which would reduce the perceived burden of their illness. Prior history of suicidal attempts increases the chance of a completed suicide by 15-fold,[21] and therefore should also always prompt a psychiatric referral. Since the risk of suicidal inclinations are only further compounded by the presence of other psychiatric comorbidities,[22] it would stand to reason that migraineurs with other psychiatric diagnoses would also need closer monitoring by a psychiatrist. Other factors like chronic pain, which increase the risk of suicidality in the general population, should be screened for in migraineurs since they will only increase the risk of suicidality. Chronic pain in general is a source of great distress that decreases quality of life, resulting in hopelessness and despair, and emergence of suicidal wishes.[23] Individuals suffering from chronic

pain may be particularly appropriate for suicide screening and intervention efforts. Two large studies, one of which studied risk of suicide in the 21–30 year age group with episodic headache and the other in 12–14 year olds with chronic daily headaches, found that the there was a significantly higher risk of suicidality in patients who experienced migraines with auras.[6,23–25] This may be due to the fact that auras make the patients more aware of their impending headache, thereby creating more distress.

Genetics are at least partially responsible for the risk of suicide as shown by twin, adoption and family based studies, but studies examining the association between specific gene variants and suicide in migraineurs have yielded inconsistent results. Reduced serotonergic activity and dysfunctions in monoamine neurotransmission has been linked with histories of suicidal behavior.[26,27] A recent study that recruited females with chronic migraines failed to show any association between MAO-A3 gene variants and suicidal risk.[28] Presumably this could be due to the small sample size employed, and further studies are required for a more comprehensive analysis.

3. If opiates are to be used in migraineurs, how might physicians protect the patients from misuse and even death and themselves from potential medical malpractice claims?

It is reported that 11.7–30% of all migraine patients use opioids.[29] Data from pain clinics estimate opioid dependence to be as high as 19%.[30] In 2010 alone, opiates were responsible for 75% of the approximately 38,000 drug overdose deaths in the United States.[31] Although not many studies elaborate on the issue of opioid misuse in migraineurs, there are studies which correctly identify that individuals with chronic pain are at a higher risk of misuse of prescribed opioids.[32–34] Many studies have observed various factors associated with opioid misuse and death, which include long acting opioids, additional psychoactive medications, additional substance use disorders, younger age, pain severity (more subjective pain, multiple pain complaints, greater pain related limitations), risk factors in three or more categories (ie, psychosocial factors, drug related factors, and genetic factors).[35–39]

Screening for opioid misuse is the cornerstone of protecting patients from drug related complications including death. Several effective screening tools exist like the Revised Screener and Opioid Assessment for Patients with Pain (SOAPP-R) or Opioid Risk Tool (ORT), but there is a dearth of validated tests or tools to reliably predict patients who are not suitable for opioid therapy or those who need increased vigilance during therapy.[35,40,41] Some self-reported questionnaires run the risk of false responses given by misusers, while some instruments are lengthy and impractical in clinical scenarios. In any case, screening should not be limited to single questionnaires and must include collateral information in the shape of testing of biologic material such as blood and urine, opioid treatment agreements, prescriptions of smaller quantities of opioids and frequent follow-ups, providing different pharmacological agents for breakthrough pain, and input from prescription monitoring programs like the Internet System for Tracking Over-Prescribing (I-STOP). New York State's I-STOP law, which was recently enforced in August 2013, is useful to ensure no multisourcing of medications and to streamline the screening process for identifying those at higher risk of opioid-associated death.[42] Opioid naïve pain patients who are at risk to abuse prescriptions might be identified by evaluating for pre and comorbid substance abuse and psychopathology.[43] Patients on opiates, who require higher doses of medications, should undergo a more thorough psychiatric evaluation at every consultation. All of the above resources should guide us with risk factor stratification and in identifying patients needing increased vigilance rather than being used to deny necessary pain treatment.

In spite of all of the above resources, opioid misuse continues to be a major public health hazard. Another valuable resource that we feel has gone largely untapped is the role of the caregiver. High risk patients should be encouraged to bring along their loved ones to physician

encounters, where both might receive information and resources to help them gain insight into the patient's condition, as is more relevant with our cases. They should be made aware of the risk of psychiatric comorbidities, opioid misuse, under-treatment and suicides, and advised about the red flags that should prompt them to seek urgent help. Contracting for safety should be encouraged to an extent that patients should be required to reach out to the physician as soon as any thoughts about suicide emerge. The implementation of directly observed treatment strategies could be employed to ensure patients adhere to a specific medication regimen and do not overdose. Establishing a therapeutic alliance similar to the 12-step Alcoholics Anonymous program could pay off huge dividends in terms of better outcomes. Pharmacological management should always be augmented by other treatment options, such as relaxation training, thermal biofeedback with relaxation training, electromyographic feedback, and cognitive behavioral therapy, which have shown to be effective in decreasing disease burden.[44,45]

Malpractice claims from chronic pain management have been on the rise. In a review by the American Society of Anesthesiologists, data collected between 2005 and 2008 revealed that 17% of 295 chronic non-cancer pain claims were related to medication management problems and death was the most common outcome in medication management claims.[46] In another study, addiction from prescribed opioids was suspected in 24% of the deaths.[47] In actuality, physicians can start by protecting themselves from malpractice claims by using the same strategies that they use to protect their patients from opioid misuse.

In an article by Rich et al that attempted to find similarities among malpractice lawsuits involving patients who overdosed on opioids, methadone, followed by hydrocodone, was found to be the leading cause of death.[48] It also pointed out that error in prescribing doses, presence of comorbid mental disorders, toxicological presence of benzodiazepines, and unrelieved pain were the most common factors in the medical records of the decedents. In some cases, opiates were started at too high a dose, titrated too rapidly, converted to other opioids incorrectly and failing to effectively screen for comorbid conditions, which could compromise therapy. Therefore, the first important strategy to protect against malpractice suits would be to make the prescriber aware of the current practices. Physicians should also be aware of potential combined adverse effects of polypharmacy and educate their patients since failure to do so has also been cited in malpractice claims.[49] Rarely P-450 "slow metabolizers" have also been known to be at a higher risk for opiate toxicity so clinicians should consider the effects of the drug utilized on the ability of the P-450 enzyme system to clear opioids. Another article stressed the importance of obtaining informed consent for the risk of iatrogenic addiction or re-addiction with chronic opioid analgesic therapy.[50] Other severe risks, such as death, should also be disclosed even when probability of occurrence is negligible. Failing to appropriately monitor patients with a past medical history significant for aberrant drug-related behaviors and substance abuse were also reasons on which malpractice claims were commonly based and so special emphasis should be placed on this aspect to protect the physician from any potential malpractice claims.

4. Tricyclics such as amitriptyline and venlafaxine are preferred migraine preventives but can also be used to overdose. Is there anything the clinician can do to prevent an overdose?

Certain antidepressants are used frequently in migraine prophylaxis, not as primary antidepressants but due to their evidence based use for the prevention of migraine. According to the recent guidelines of episodic migraine, both drugs have level B evidence for their usage. However, all medications have risks in association with them. All antidepressants (and antiepileptic medications for that matter) are labeled with increased risk of suicidality. According to several small studies,[51,52] the use of venlafaxine may be associated with a greater risk of suicide than SSRIs. One of the studies suggests that the use of amitriptyline shows no greater

risk than the use of other antidepressants in a group of people being treated for suicidality.[52] It is worth noting that tricyclics have a fairly narrow therapeutic index and overdose with these medications may be easier than with other medications. It does suggest that the use of these medications should be closely monitored. The practitioner should monitor for worsening mood, suicidality, inappropriate usage or dosing of these medications and use of concurrent medications or illicit substances. If necessary, shorter follow-up times, pill counts, or having a family member or caregiver dispense medications could also be considered.

5. In case 2, how do you distinguish an overdose from a suicide?

Opioids have become one of the more common class of drugs associated with accidental fatal poisoning. However, the true numbers of deaths due to an accidental overdose and suicide are unknown largely due to misclassification or lack of classification of intent.[51–54] Due to the same reason, studies conducted in this regard have been difficult to interpret. One method was to question overdose survivors with substance abuse disorders about their intentions at the time of overdose. A review of studies which employed that method indicated that only a minority of overdoses were reported to be intentional.[55] Having said that, a number of qualitative studies indicate that "intentional overdose" may not be equivalent to "suicide,"[56] further complicating the interpretation of such studies. There is some evidence that individuals intending to commit suicide via overdose are unlikely to use their usual drug of choice or use a much higher dose than that which they usually take.[57,58] With the publication of the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM), many of the numerous opioid abuse disorders have been simplified and condensed under the term opioid use disorders. This may change the way we perceive or analyze data since previous studies used DSM-4 or earlier diagnostic criteria.

Determining whether an overdose was suicidal or accidental often depends on the circumstances surrounding the death. Indicators of suicide include previous suicide attempts, sudden negative life events, saving pills so as to have a lethal dose on hand, or "preparing" for one's death by writing a will, etc.

Individuals contemplating suicide usually display signs of needing help largely by threatening to commit suicide or if all else fails could leave a suicide note. If there are no red flags such as the one described above, authorities will usually assume that death occurred as a result of overdose, like in our case. On a biological level, overdose can be particularly confusing since organisms learn to make responses that attenuate the effect of the drug in the presence of cues previously paired with the drug. This would explain the "failures" of tolerance that occur when a drug-experienced individual suffers an "overdose."[59–61] Pavlovian conditioning resulting in situation-specific tolerance is capable of leading to overdose in a non-familiar setting and accidental overdose. It is important to keep in mind that not all overdoses are intentional and not all intentional overdoses are necessarily suicide attempts.

REFERENCES

1. Pompili M, Serafini G, Martelletti P, et al. Psychiatric comorbidity and suicide risk in patients with chronic migraine. *Neuropsychiatr Dis Treat.* 2010; 6:81-91.
2. Shapiro R, Goadsby P. The long drought: The dearth of public funding for headache research. *Cephalalgia*. 2007;27:991-994.
3. Adams AM, Serrano D, Lipton R, et al. The impact of chronic migraine: The chronic migraine epidemiology and outcomes (CaMEO) study methods and baseline results. *Cephalalgia* 2015;35: 563-578.
4. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: Investigating potential etiology and prognosis. *Neurology* 2003;60:1308-1312.
5. Patel NV, Bigal ME, Kolodner KB, Leotta C, Lafata JE, Lipton RB. Prevalence and impact of migraine and probable migraine in a health plan. *Neurology* 2004;63:1432-1438.
6. Breslau N, Davis GC, Andreski P. Migraine, psychiatric disorders, and suicide attempts: An epidemiologic study of young adults. *Psychiatry Res.* 1991;37:11-23.
7. Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of migraine and psychiatric

disorders—A national population-based study. *Headache* 2008;48:501-516.
8. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life, and depression: A population-based case-control study. *Neurology* 2000;55:629-635.
9. Zwart JA, Dyb G, Hagen K, Dahl AA, Bovim G, Stovner LJ. Depression and anxiety disorders associated with headache frequency. The Nord-Trondelag health study. *Eur J Neurol* 2003;10: 147-152.
10. McWilliams LA, Goodwin RD, Cox BJ. Depression and anxiety associated with three pain conditions: Results from a nationally representative sample. *Pain* 2004;111:77-83.
11. Victor TW, Hu X, Campbell J, White RE, Buse DC, Lipton RB. Association between migraine, anxiety and depression. *Cephalalgia* 2010;30:567-575.
12. Ilgen MA, Zivin K, McCammon RJ, Valenstein M. Pain and suicidal thoughts, plans and attempts in the United States. *Gen Hosp Psychiatry* 2008; 30:521-527.
13. Ratcliffe GE, Enns MW, Belik SL, Sareen J. Chronic pain conditions and suicidal ideation and suicide attempts: An epidemiologic perspective. *Clin J Pain* 2008;24:204-210.
14. Fuller-Thomson E, Schrumm M, Brennenstuhl S. Migraine and despair: Factors associated with depression and suicidal ideation among Canadian migraineurs in a population-based study. *Depress Res Treat.* 2013;401487.
15. Cambell G, Darke S, Bruno R, Degenhardt L. The prevalence and correlates of chronic pain and suicidality in a nationally representative sample. *Aust N Z J Psychiatry* 2015;49:803-811.
16. Sheehan DV, Lecrubier Y, Dunbar GC, et al. The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59(Suppl. 20):22-33.
17. Kanner AM. Are antiepileptic drugs used in the treatment of migraine associated with an increased risk of suicidality? *Curr Pain Headache Rep.* 2011; 15:164-169.
18. Friedman RA. Antidepressants' black-box warning—10 years later. *N Engl J Med.* 2014;371:1666-1668.
19. CDC. National Suicide Statistics at a Glance. Injury Center: Violence Prevention 2013 April 2, 2013. Available from: http://www.cdc.gov/violence-prevention/suicide/statistics/rates02.html.
20. Scocco P, de Girolamo G, Pavan L. Suicide phenomena in nursing homes: A neglected issue in geriatric research and clinical management? *J Am Geriatr Soc.* 2006;54:1299-1300.
21. Kennedy SP, Baraff LJ, Suddath RL, Asarnow JR. Emergency department management of suicidal adolescents. *Ann Emerg Med.* 2004;43:452-460.
22. De Filippis S, Erbuto D, Pompili M, et al. Mental turmoil, suicide risk, illness perception, and temperament, and their impact on quality of life in chronic daily headache. *J Headache Pain* 2008;9: 349-457.
23. Pompili M, Di Cosimo D, Innamorati M, Lester D, Tatarelli R, Martelletti P. Psychiatric comorbidity in patients with chronic daily headache and migraine: A selective overview including personality traits and suicide risk. *J Headache Pain* 2009; 10:283-290.
24. Wang SJ, Fuh JL, Lu SR, Juang KD. Chronic daily headache in adolescents: Prevalence, impact, and medication overuse. *Neurology* 2006;66:193-197.
25. Wang SJ, Juang KD, Fuh JL, Lu SR. Psychiatric comorbidity and suicide risk in adolescents with chronic daily headache. *Neurology* 2007;68:1468-1473.
26. McGuffin P, Marusic A, Farmer A. What can psychiatric genetics offer suicidology? *Crisis* 2001;22:61-65.
27. Brezo J, Klempan T, Turecki G. The genetics of suicide: A critical review of molecular studies. *Psychiatr Clin North Am* 2008;31:179-203.
28. Serafini G, Pompili M, Martelletti P, et al. Gene variants with suicidal risk in a sample of subjects with chronic migraine and affective temperamental dysregulation. *Eur Rev Med Pharmacol Sci.* 2012; 16:1389-1398.
29. Buse DC, Pearlman SH, Reed ML, Serrano D, Ng-Mak DS, Lipton RB. Opioid use and dependence among persons with migraine: Results of the AMPP study. *Headache* 2012;52:18-36.
30. Fishbain DA, Rosomoff HL, Rosomoff RS. Drug abuse, dependence, and addiction in chronic pain patients. *Clin J Pain* 1992;8:77-85.
31. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. *J Am Med Assoc.* 2013;309:657-659.
32. Solanki DR, Koyyalagunta D, Shah RV, Silverman SM, Manchikanti L. Monitoring opioid adherence

in chronic pain patients: Assessment of risk of substance misuse. *Pain Physician* 2011;14:E119-E131.
33. Gourlay DL, Heit HA. Pain and addiction: Managing risk through comprehensive care. *J Addict Dis.* 2008;27:23-30.
34. Denisco RA, Chandler RK, Compton WM. Addressing the intersecting problems of opioid misuse and chronic pain treatment. *Exp Clin Psychopharmacol.* 2008;16:417-428.
35. Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: A review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician* 2012;15(Suppl. 3):ES67-ES92.
36. Ballantyne JC. Opioid analgesia: Perspectives on right use and utility. *Pain Physician* 2007;10:479-491.
37. Liebschutz JM, Saitz R, Samet JH, et al. Clinical factors associated with prescription drug use disorder in urban primary care patients with chronic pain. *J Pain* 2010;11:1047-1055.
38. Papaleontiou M, Henderson CR Jr, Reid MC, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: A systematic review and meta-analysis. *J Am Geriatr Soc.* 2010;58:1353-1369.
39. Jamison RN, Link CL, Marceau LD. Do pain patients at high risk for substance misuse experience more pain? A longitudinal outcomes study. *Pain Med.* 2009;10:1084-1094.
40. Butler SF, Fernandez K, Benoit C, Budman SH, Jamison RN. Validation of the revised screener and opioid assessment for patients with pain (SOAPP-R). *J Pain* 2008;9:360-372.
41. Webster L, Russell M, Adefehinti F, Dalgarno EJ, Moffat CF. Preliminary assessment of polybrominated diphenyl ethers (PBDEs) in the Scottish aquatic environment, including the Firth of Clyde. *J Environ Monit.* 2008;10:463-473.
42. Sharp MJ, Melnik TA. Poisoning deaths involving opioid analgesics—New York state, 2003-2012. *MMWR Morb Mortal Wkly Rep.* 2015;64:377-380.
43. Cicero TJ, Lynskey M, Todorov A, Inciardi JA, Surratt HL. Co-morbid pain and psychopathology in males and females admitted to treatment for opioid analgesic abuse. *Pain* 2008;139:127-135.
44. Aukerman G, Knutson D, Miser WF. Management of the acute migraine headache. *Am Fam Physician*, 2002;66:2123-2130.
45. Sierpina V, Astin J, Giordano J. Mind-body therapies for headache. *Am Fam Physician* 2007;76:1518-1522.
46. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. *Anesthesiology* 2011;114:918-926.
47. Fitzgibbon DR, Rathmell JP, Michna E, Stephens LS, Posner KL, Domino KB. Malpractice claims associated with medication management for chronic pain. *Anesthesiology* 2010;112:948-956.
48. Rich BA, Webster LR. A review of forensic implications of opioid prescribing with examples from malpractice cases involving opioid-related overdose. *Pain Med.* 2011;12(Suppl. 2):S59-S65.
49. Fishbain, DA, Lewis JE, Gao J. Allegations of medical malpractice in chronic opioid analgesic therapy possibly related to collaborative/split treatment and the P-450 enzyme system: Forensic case report. *Pain Med.* 2010;11:1419-1425.
50. Fishbain DA, Lewis JE, Gao J. Medical malpractice allegations of iatrogenic addiction in chronic opioid analgesic therapy: Forensic case reports. *Pain Med.* 2010;11:1537-1545.
51. Taylor D, Lenox-Smith A, Bradley A. A review of the suitability of duloxetine and venlafaxine for use in patients with depression in primary care with a focus on cardiovascular safety, suicide and mortality due to antidepressant overdose. *Ther Adv Psychopharmacol.* 2013;3:151-161.
52. Coupland CHT, Morriss R, Arthur A, et al. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: Cohort study using a primary care database. *Br Med J.* 2015;350:517.
53. Rockett IR, Hobbs G, Walker RL, et al. Suicide and unintentional poisoning mortality trends in the United States, 1987-2006: Two unrelated phenomena? *BMC Public Health* 2010;10:705.
54. Rockett IR, Wang S, Kapusta ND, et al. Race/ethnicity and potential suicide misclassification: Window on a minority suicide paradox? *BMC Psychiatry* 2010;10:35.
55. Breiding MJ, Wiersema B. Variability of undetermined manner of death classification in the US. *Inj Prev.* 2006;12(Suppl. 2):ii49-ii54.
56. Cheatle MD. Depression, chronic pain, and suicide by overdose: On the edge. *Pain Med.* 2011; 12(Suppl. 2):S43-S48.
57. Bohnert AS, Roeder K, Ilgen MA. Unintentional overdose and suicide among substance users: A

review of overlap and risk factors. *Drug Alcohol Depend.* 2010;110:183-192.
58. Neale J. Suicidal intent in non-fatal illicit drug overdose. *Addiction* 2000;95:85-93.
59. Darke S, Ross J. The relationship between suicide and heroin overdose among methadone maintenance patients in Sydney, Australia. *Addiction* 2001;96:1443-1453.
60. Brådvik L, Berglund M, Frank A, Lindgren A, Löwenhielm P. Number of addictive substances used related to increased risk of unnatural death: A combined medico-legal and case-record study. *BMC Psychiatry* 2009;9:48.
61. Siegel S, Hinson RE, Krank MD, McCully J. Heroin "overdose" death: Contribution of drug-associated environmental cues. *Science* 1982;216:436-437.