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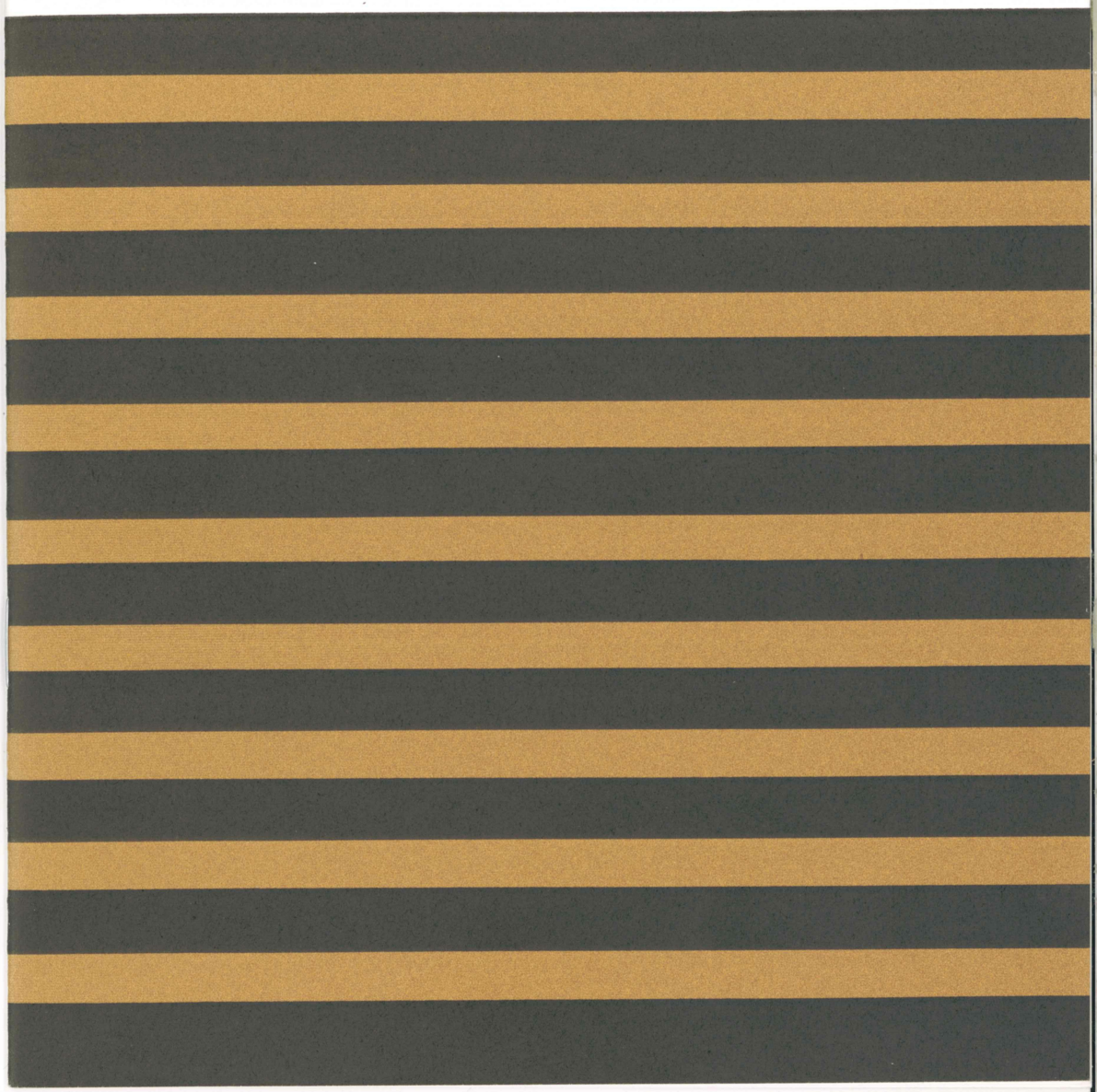

Off-label prescribing of antidepressants and anxiolytics: an attorney's guide to psychoactive drugs

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"Off-label" prescribing of psychoactive drugs for indications other than those approved by the FDA is a common practice among psychiatrists as well as general practitioners. A major off-label use is the prescription of sedating antidepressants for sedative–hypnotic purposes. This practice is examined, and the major categories of antidepressant, anxiolytic, and hypnotic medications are explored, based on their FDA-approved indications as well as common usage. The implications for physician and hospital liability for this practice are reviewed. The off-label usage of antidepressants for the treatment of non-depressed alcoholics is also reviewed, and on-line research tools for attorneys to obtain updated information in this area are evaluated.

In "off-label" prescribing,[1] a quite common practice among physicians, a drug approved by the U.S. Food and Drug Administration for one or more specified indications is in fact prescribed to treat other symptoms or diseases for which reg-

ulatory authority has not been obtained, but for which evidence of varying reliability is available to the clinician for the safety and efficacy of the drug for the condition. In the area of psychopharmacology, "many off-label uses have been proven [safe & efficacious] beyond a reasonable doubt."[2] While there have been no regulations affecting the practice of off-label prescribing until quite recently (see below), this article concentrates on the relatively common practice among psychiatrists as well as general practitioners of prescribing sedating antidepressants for primary insomnia, an indication for which no currently available antidepressant has been approved. The article also provides necessary background on the categories, usage, and potential for liability associated with drugs used to treat depression and insomnia. The article does not discuss other categories of psychoactive medications that have also been frequently prescribed off-label, such as drugs from the antipsychotic and mood-stabilizer classes.

Regulation of off-label uses

The FDA has published for comment a proposed rule implementing provisions of Section 401 of the Food and Drug Administration Modernization Act of 1997[3] that under certain specific circumstances will permit drug manufacturers to disseminate written information concerning the safety, effectiveness, or benefits of a use not described in the product's approved labeling.[4] Prior to the enactment of this legislation, the dissemination of such information could have been considered "promotion" of an unapproved use, in violation of the Federal Food, Drug and Cosmetic Act.[5] The act's prohibitions in this regard applied only to drug manufacturers rather than to prescribing physicians, so physicians have been free to prescribe "off-label," subject only to liability for medical malpractice under state law if the act of prescribing failed to meet the requisite standard of care in force in the jurisdiction. A commonly applied standard in such circumstances is that

FDA approval of indication and dosage can provide substantial but not conclusive proof that a drug was properly prescribed, as is discussed more fully below. Many of the cross-uses of sedating antidepressants for insomnia or anxiety, as discussed in this article, are examples of such common off-label prescribing, and they may be affected by the new rule's allowing the manufacturer to support such prescribing if adequate justification is provided. It remains to be seen, however, whether the rule will operate to create a "safe harbor" to protect the prescribing physician from claims arising from ill effects of the use of medication for non-FDA-approved indications. In the case of the use of sedating antidepressants for primary insomnia, it also remains to be seen whether drug manufacturers will attempt to promote such use with the requisite supporting studies. As will be seen below, few such studies exist in the published literature. Moreover, because three of the antidepressants most commonly prescribed for insomnia (amitriptyline, doxepin and trazodone) have obtained generic status, there may be no financial incentive for the original patent holder to promote the off-label use or fund the additional studies necessary to gain FDA approval under the new regulatory regime.

Categories of psychotropic medication

Although the terminology for the classification of drugs used for psychiatric purposes has evolved, so that currently obsolete terminology may appear in earlier reported case law (e.g., major and minor tranquilizers), the classification of diagnoses set forth in the current standard reference work, the *Diagnostic and Statistical Manual–IV* of the American Psychiatric Association (DSM–IV), as well as current clinical practice, has resulted in the following major categories descriptive of medication used to treat psychiatric conditions relevant to this article.

1. Antidepressants

The usage of antidepressants is widespread and has grown substantially in recent years. Factors leading to this increase include wider recognition of the extent of depression in the adult population, and the education of primary care providers in the diagnosis and treatment of the disorder. Perhaps the foremost factor driving their greater use has been the introduction and widespread availability of newer classes of agents with side-effects profiles offering improved safety and patient tolerability as compared with earlier drugs (and procedures such as electroconvulsive therapy) used to treat depression prior to the late 1980s.

Classic agents: tricyclics and MAOIs

First introduced in the late 1960s, tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) gained acceptance for use with both hospitalized and outpatient depressives. They are still available today, but because of side-effect and safety issues compared with newer agents such as the SSRIs discussed below, their usage to treat depression has substantially declined. They are now more frequently prescribed as second- or third-line agents for depression resistant to treatment with the newer classes of antidepressants or, in the case of the tricyclics, for the management of symptoms for which their side effects are of value, most prominently including sedation for insomnia and anxiety and for chronic-pain relief. Because of potentially dangerous interactions with many substances commonly found in food,[6] use of the monoamine oxidase inhibitors has been limited to treatment-resistant depression and for social phobia. For these reasons we will turn our attention to the TCAs and then to the newer agents.

Available research suggests a complex relationship between TCA medications and neuropsychological impairment.[7] Of the group, only amitriptyline and, to a lesser extent, imipramine have shown reasonable evidence of sustained neuropsychological effects, which effects may diminish as tolerance develops, particularly among younger subjects.[8]

Tricyclics (TCAs) include the following currently available in the U.S., in order of introduction: imipramine; amitriptyline, doxepin, trimipramine, nortriptyline, desipramine, and protriptyline. Allegations of psychiatric malpractice involving the prescription of TCA antidepressants[9] can fall into two categories: (1) suicide from overdose caused by prescribing too large a dosage or providing too many doses with one prescription of a TCA (TCAs are lethal in quantities exceeding their therapeutic level) or (2) suicide brought on by the effects of the antidepressant medication itself, which claims have also been brought in connection with newer agents, with fluoxetine (Prozac) having gained the most public notoriety. Because the toxic levels of TCAs exceed the efficacious levels by only a relatively small margin, their use has fallen out of favor for depressed individuals whose work-up indicates any potential for suicide. They have been largely replaced in this population, as well as in others, for the reasons discussed above, by the newer agents described below. That the TCAs remain problematic from a health and liability perspective can be seen from two recent cases: *Winger v. Franciscan Medical Center and Danilo*[10] (amitriptyline overdose led to psychiatrist and hospital liability); *Hobart v. Shin*[11] (prescribing psychiatrist could assert an affirmative defense of contributory negligence to an action brought by the estate of a patient who committed suicide by taking an overdose of doxepin, which the defendant had prescribed in a quantity sufficient to allow the patient to overdose). Thus the search for newer agents was driven in part by the relatively high potential toxicity of the TCAs.

Selective serotonin reuptake inhibitors

SSRIs currently approved in the U.S. for depression, in order of their introduction, include fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil),[12] and citalopram[13] (Celexa). Fluvoxamine (Luvox) has been approved for use in obsessive-compulsive disorder but is also frequently prescribed as an antidepressant. These agents are generally not approved for or generally utilized for insomnia that is not secondary to

depression; sometimes the SSRIs themselves can induce insomnia, in which case additional medication may be required. In fact, trazodone, which has become the most widely prescribed antidepressant for primary insomnia, has been validated in clinical trials for SSRI-induced insomnia, while its use for primary insomnia is based on far sketchier data, as noted below.

Newer, dual action, and atypical antidepressants

Trazodone (Desyryl) was the first antidepressant approved in the U.S. that was neither a TCA nor an MAOI. It is currently viewed by many practitioners, however, as less effective for depression than other available agents. It is now more widely prescribed as a hypnotic than as an antidepressant,[14] in doses lower than indicated for depression, for both nondepressed patients and as an adjunct for SSRI-induced insomnia.[15-19] It is now likely the most widely prescribed hypnotic for chronic or antidepressant-induced insomnia. Only quite recently, however, was the first report published evaluating the effect of trazodone on the sleep of nondepressed insomniacs.[20]

Nefazodone (Serzone), approved in 1996 for depression, is structurally similar to trazodone but less sedating. Recent research, however, indicates that it too may be useful for insomnia, in both nondepressed and depressed individuals, and does not disturb sleep as is often the case with the SSRIs.

Venflaxamine (Effexor) was introduced in 1995. It operates on both serotonin and norepinephrine brain receptor systems and is thus referred to as a dual-acting rather than a selective serotonin reuptake inhibitor. Mirtazapine (Remeron), the newest antidepressant approved in the U.S., also exhibits dual action, but it is much more sedating than the other dual agents and thus is useful for depressed patients who exhibit prominent insomnia and/or anxiety as a presenting symptom. It is also being investigated for use as a hypnotic in nondepressed insomniacs.[21] Paradoxically, lower rather than higher doses appear to have greater hypnotic efficacy.

2. Sedatives/ anxiolytics

Formerly referred to as tranquilizers, the oldest and best-known agents from this class include diazepam (Valium) and chlordiazepoxide (Librium). As will be seen below, they also have off-label usage as hypnotics, and in fact all benzodiazepines have hypnotic efficacy if used in sufficient dosages.

3. Hypnotics

Although older "sleeping pills," including barbiturates and chloral hydrate, are still available, they have largely been replaced in most states by benzodiazepines,[22] which are far safer in overdose, although they too may lead to physiological dependence and a withdrawal syndrome.[23] In turn, benzodiazepines are being replaced for hypnotic use by drugs from structurally different classes that also work on the benzodiazepine brain receptor, but in a more selective fashion. That is, they preferentially bind to the omega-1 BZD sub-receptor, which induces sleep but does not share the anti-anxiety and anticonvulsant activities of benzodiazepine. This selectivity is thought to reduce the abuse potential, addiction, rebound insomnia and memory deficit problems associated with benzodiazepines.

Benzodiazepines currently approved by the FDA for marketing as hypnotics, in order of their introduction, include flurazepam (Dalmane), temazepam (Restoril), triazolam (Halcion), estazolam (ProSom), and quazepam (Doral). These compounds can be categorized by their length of action (half-life) and other pharmacokinetic measures that influence the onset and duration of hypnotic action, as well as any carry-over daytime sedative and performance-degrading effects. Anterograde amnesia can be a problem, and because of negative publicity and legal liability surrounding this class, most particularly with Halcion, it is unlikely that further products from the class will be introduced in the U.S. It may be noted that the parent compound of Doral and one of its longer-acting metabolites is claimed to be omega-1 selective—indeed, to a greater degree than zolpidem as discussed below[24]—but another long-acting metabolite is similar to that produced by Dalmane[25] and thus may accumulate with repeated adminis-

tration to produce unwanted sedative effects and performance decrements.

Other benzodiazepines not approved for marketing for hypnotic use but nonetheless widely utilized for this purpose[26] include lorazepam (Ativan), clonazepam (Klonopin), oxazepam (Serax), and chlordiazepoxide (Librium).

The first agent of the new class, zolpidem (Ambien),[27] is nonetheless classified by the FDA in the same control class (Schedule IV) as benzodiazepines, so there are prescribing restrictions applicable to zolpidem as well. Zolpidem has a rapid onset of action and a very short half-life; these characteristics may contribute to its lack of next-day sedation or memory deficits when compared with those associated with longer-acting hypnotic agents, but they may limit its usefulness in cases of sleep-maintenance or early-morning-awakening insomnia. Since these types of insomnia are often associated with depression, the sedating antidepressants are often used in place of hypnotics in such individuals. Ambien is currently one of the most prescribed drugs in the U.S.

Another agent of this class, zolpiclone (Imovane), is available in Canada and many other countries but not in the U.S. It has a longer half-life than zolpidem. By contrast, the next agent of this class, zaleplone,[28] which is currently in Stage III trials before the FDA, has an even shorter half-life than zolpidem, as do other investigational pyrazolopyrimidine hypnotics. The manufacturer believes this will provide a marketing advantage over zolpidem, the labeling of which currently warns that it should not be taken unless the consumer expects to remain in bed for at least seven hours. There are reports in the literature of anterograde amnesia by those taking zolpidem, having to awake in the middle of the night and having no memory of the events that took place while awake.

Sedating antidepressants also commonly prescribed as hypnotics, while lacking FDA approval for this indication,

include doxepin,[29] amitriptyline, and trimipramine[30] among the TCAs, and trazodone and mirtazapine among the newer antidepressants. There is evidence that nefazodone, while not particularly sedating, may be of utility for sleep maintenance rather than sleep induction insomnia.[31]

Physician liability for off-label prescribing

Courts in all jurisdictions generally recognize the propriety of off-label prescribing. See, e.g., *Washington Legal Foundation v. Kessler;*[32] *Rhone-Poulenc Rorer Pharm., Inc. v. Marion Merrill Dow, Inc.;*[33] *Haynes v. Baton Rouge Gen. Hosp.*[34] A drug manufacturer's instructions regarding the administration of a medication, including the indications therefor, are admissible as evidence to establish the standard of care owed by the prescribing physician. Some courts have held that a plaintiff may establish elements of a prima facie case using the instructions, without the necessity of the expert testimony that would otherwise be required to establish the standard of care in medical malpractice cases. *Ohlingschlager v. Proctor Community Hospital;*[35] *Mulder v. Parke Davis & Co.*[36] Case law has been mixed, however, as to whether a drug manufacturer's package insert, as printed in the *Physician's Desk Reference* and as approved by the FDA, can alone be sufficient to establish the standard of care absent expert testimony. Compare *Witherell v. Weimer*[37] (*PDR* warning can provide proof of professional standard ordinarily required to be shown by expert testimony) with *Mielke v. Condell Memorial Hospital*[38] (court could find no case from any jurisdiction permitting package insert or *PDR* passage alone to constitute sufficient evidence of the standard of care) and *Ellington v. Bilsel*[39] (evidence demonstrating that *adherence* to *PDR* recommendations was the standard of care is necessary for plaintiff's case). If adherence to the manufacturer's instructions as to indications is insufficient to establish the standard of care, one can take the position that such instructions are not conclusive as to the proper utilization of the medication,

and thus off-label prescribing is not necessarily violative of the standard of care.

As there appears to have been little litigation resulting from the off-label prescribing of antidepressants or anxiolytics for insomnia in nondepressed patients, one can assume that their use in this fashion has been relatively safe, and that established texts and journal articles[40] recommending their use could be used effectively by defendants to rebut a plaintiff's assertion that the off-label use in and of itself should adequately characterize a violation of the standard of care. Compare *Proctor v. Davis*[41] (physician's testimony that he was unaware that the drug was not approved for a particular use was irrelevant in strict products liability action); as modified on remand[42] (drug manufacturer, and not physician, had duty to warn of risks attendant to off-label use where manufacturer was in possession of such knowledge).

Pharmacotherapy for alcoholism

As there were few FDA-approved pharmacological treatments for alcoholism until quite recently, off-label usage was common, often involving various combinations of antidepressants, sedatives and hypnotics. This practice should change with the addition of two agents recently approved specifically for reducing the craving of detoxified alcoholics, who previously were often offered only psychotherapeutic support, group counseling, or informal groups such as AA. Naltrexone (Revia), which blocks opiate receptors and had been previously utilized (as Trexan) for maintenance treatment of detoxified opiate addicts, was more recently shown to reduce craving in alcoholics; for a recent review see Salloum et al., "Naltrexone Utility in Depressed Alcoholics."[43] European Union approval was recently granted for acamprosate (Campral in the U.K.), which is still under FDA review in the U.S. See Schneider et al., "Maintenance of Abstinence in Alcoholics."[44] Prior to the introduction of these agents, the

only medication available to the U.S. practitioner was disulfiram (Antabuse), which had a behavioral mode of action by inducing violently unpleasant symptoms when alcohol was ingested. Patient compliance has been poor, and studies have failed to document the efficacy of this agent for chronic alcoholism.

Research techniques

Attorneys researching information concerning specific psychotropic medications now have available to them the resources of the National Institute of Health's compilation of abstracts of numerous medical journals on-line, MEDLINE, available without charge on the Internet at http://www.nim.nih.gov/. Attorneys should be aware, however, that MEDLINE has significant limitations of coverage with respect to psychoactive drugs, in that articles appearing in many journals, such as *Human Psychopharmacology* and *Experimental & Clinical Psychopharmacology,* and Ph.D. dissertations are not abstracted in MEDLINE. A broader on-line abstracting service that reveals more articles concerning a given psychoactive substance is found in *Psych Info*; this is available on a fee basis through on-line services such as Ovid and CompuServe's IQ Quest, which charges a usage fee in addition to the standard monthly fixed rates for subscribers to the on-line service. See also editorial "Medical Information on the Internet."[45]

Conclusion

Off-label prescribing of sedating antidepressants for hypnotic use in nondepressed patients is a common practice, albeit one lacking rigorous support to date in the published literature. Use of the newer agents such as trazodone for this purpose has not led to any reported cases of liability for the prescriber, in contrast to the TCAs, where deaths have resulted

from their usage in clinical depression. It will be of interest to see if this common practice will be affected by the new FDA rules for off-label claims, or whether the fact that most of these agents have lost patent protection, and that even for drugs still enjoying patent protection the substantial cost of studies to obtain approval for new indications, will mean that few applications to market a product already well accepted in clinical practice will cross FDA's transom.

Notes

1. See, e.g., Beck, JM & Azari, ED, FDA, off-label use, and informed consent, 53 *Food and Drug Law J.*, 71, 76-80 (1998).
2. Janik et al., *Principles and Practice of Psychopharmacology* at 56 (2d ed. 1997).
3. Public Law 105-115.
4. 63 *Fed. Reg.* 31143-31161 (June 8, 1998). The rules took effect on November 21, 1998. That FDA approval may not readily be granted under this authority can be gleaned from the FDA's rejection of numerous health and nutritional claims from supplement manufacturers under existing statutory authority granted in Sections 303 and 304 of the same Modernization Act amendments. See, e.g., 63 *Fed. Reg.* 34107 (June 22, 1998) (rejecting claims that omega-3 fatty acids reduce the risk of cardiovascular disease).
5. 21 U.S.C. 321 *et seq.*
6. Jefferson, Drug and diet interactions: avoiding therapeutic paralysis, 59 *J. Clin. Psychiatry* (Supp. 16), 31-39 (1998).
7. Hartman, *Neuropsychological Toxicity* at 274 on (2d ed. 1995).
8. Depulta and Pomara, Effects of antidepressants on human performance: A review, 10 *J. of Clinical Psychopharmacology*, 105-111 (1990).
9. Daly, Medico-legal aspects of prescribing, 9 *Human Psychopharmacology*, 35-36 (1994).
10. No. 3-97-0680 (Ill. App. Sept. 24, 1998).
11. No. 84667 (Ill. S. Ct. Dec. 17, 1998), reversing 292 Ill. App. 3d 580, 686 N.E. 2d 617 (1997).
12. See Dunner & Kulman, Paroxetine, a review of clinical experience, 31 *Pharmacopsychiatry* 89-101 (May 1998).

13. Highly selective SSRI approved by FDA for depression, 26 *Clinical Psychiatry News* 9:1, 6-7 (October 1998).

14. Thase, ME, Depression, sleep and antidepressants. 59 *J. of Clin. Psychiatry* (Supp. 4), 62 (1998).

15. Yamadera, Effects of trazodone hydrochloride and imipramine on polysomography in healthy subjects, 52 *Psychiatry and Clinical Neuroscience,* 435-443 (1998).

16. Sharf, MB and Sachais, BA, Sleep laboratory evaluation of the effects and efficacy of trazodone in depressed insomniac patients, 51 *J. Clin. Psychiatry,* 13-17 (1990).

17. Ware, JC and Pittard, JT, Increased deep sleep after trazodone use: A double-blind placebo-controlled study in healthy young adults, 51 *J. Clin. Psychiatry*, 18-22 (1990).

18. Okino, H, Sugawara, K, Yagasaki, N et al., Effects of trazodone on nocturnal sleep, 6 *Psychosom. Ther.*, 61-89 (1994) (in Japanese).

19. Montgomery, I, Oswald, I, Morgan, K, Adam, K, Trazodone enhances sleep in subjective quality but in objective duration, 16 *Br. J. Clin. Pharmacol.*, 139-144 (1983).

20. Walsh, JK et al., Subjective hypnotic efficacy of trazodone and zolpidem in DSM III-R primary insomnia, 13 *Human Psychopharmacology*, 191-198 (June 1998).

21. Sennef, C et al., Effects of mirtazapine, amitriptyline, and their combination on sleep in healthy volunteers. Poster presentation, Organon, NV, 1998.

22. In some states, notably New York, benzodiazepine prescribing is subject to rigorous regulation, including a requirement for triplicate copies of prescriptions. Paradoxically this has led to an increased utilization of the older hypnotics, which are not regulated in this fashion.

23. Schweizer and Rickels, Benzodiazepine dependence and withdrawal: A review of the syndrome and its clinical management, 98 *Acta Psychiatrica Scandinavia* (Supp. 393), 95 (1998).

24. Rush, CR et al., Benzodiazepine recepter ligands in humans: Acute performance-impairment and subject-rated effects, 18 *Journal of Clinical Psychopharmacology*, 154-166 (April 1998).

25. Hunt, TL et al., Comparison of 24-h plasma concentrations of the N-desalkyl metabolite of quazepam and flurazepam in a single-dose study, 3 *J. Pharm. Med.*, 3-9 (1993).

26. Kupfer and Reynolds, Current concepts: Management of insomnia, 336 *New England J. of Med.*, 341, 343 (Jan. 30, 1997).

27. Rush, Behavioral pharmacology of zolpidem relative to benzodiazepines: A review, 61 *Pharmacol. Biochem. Behav.*, 253-269 (Nov. 1998).

28. Sakamole, K et al., Efficiency of L-846 in patients with insomnia: Evaluation by poly-somnography, 52 *Psychiatry and Clinical Neuroscience*, 156-157 (1998).

29. Hajak, *Doxepin Improves Sleep in Primary Insomnia* (in press).

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31. Verman, NP et al., Nefazodone is effective in the treatment of insomnia [abstract], 21 *Sleep* 302 (Supp. 1998).

32. 880 F. Supp. 26, 28 n.1 (D.D.C. 1998).

33. 93 F. 3d 511, 514 n.3 (8th Cir. 1996).

34. 298 So. 2d 149, 153 (La. App. 1974).

35. 55 Ill. 2d 411 (1973).

36. 288 Minn. 232 (1970).

37. 118 Ill. 2d 321 (1987).

38. 124 Ill. App. 3d 42 (1984).

39. 255 Ill. App. 3d 233 (1993).

40. See, e.g., the text cited *supra*, n.1 and references therein, the articles cited in this review, and American Psychiatric Association, *Textbook of Psychopharmacology* (2d ed. 1998).

41. 275 Ill. App. 3d 593, 656 N.E. 2d 23, 32 (1995).

42. 291 Ill. App. 3d 265, 682 N.E. 2d 1203 (1997).

43. 34 *Psychopharmacology Bulletin*, 111-115 (1998).

44. 31 *Pharmacopsychiatry*, 110-113 (1998).

45. 280 *Journal of the American Medical Association*, 1363 (October 21, 1998).