Maintenance Treatment of Insomnia: What Can We Learn From the Depression Literature?

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Insomnia and depression are common problems with profound public health consequences. When left untreated, both conditions have high rates of persistence and recurrence. Maintenance treatment for depression is fairly well established, but there is no evidence-based consensus regarding the safety and efficacy of maintenance therapy for insomnia. Consequently, long-term treatment of insomnia is driven primarily by the individual choices of patients and their clinicians. This article compares and contrasts the current state of research in the maintenance therapy of depression and insomnia and highlights gaps in the insomnia literature.

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Insomnia is increasingly seen as a major public health concern. An estimated 10%–35% of the general population reports symptoms of insomnia (1–4). Insomnia is associated with high rates of medical disorders (1), psychiatric disorders (5), work absenteeism (6), and accidents (7, 8). Moreover, data from the National Institute of Mental Health's Epidemiological Catchment Area (ECA) study suggest that even insomnia that is unrelated to any other psychiatric disorder is associated with greater use of general medical and psychiatric services (9). Overall, the annual direct and indirect costs related to insomnia have been estimated to total between 30 and 35 billion in 1994 dollars (10).

A number of epidemiological and clinical studies indicate that untreated insomnia has high rates of recurrence and persistence. For example, in a prospective study, Ganguli and colleagues found that insomnia is a chronic problem among older adults (11). In another study, most of the patients continued to have insomnia after 64 months (12). Similarly, a 7-year follow-up study of a cohort of a Swiss population, ages 20 and 21, showed that 8%–10% of the population continued having insomnia and 13%–19% continued having repeated brief insomnia (13, 14). Prospective studies of patients with general medical conditions also showed that complaints of insomnia tend to be persistent or recurrent over time (15, 16). Thus, it seems that patients with chronic insomnia need some form of treatment.

Various surveys in the community and primary care suggest that 2%–6% of the population use medications for sleep, and such use seems to increase with age (1, 17). A significant proportion of these people continue to take sleep medication over long periods of time (18), even though current prescribing guidelines recommend limiting sleep medication to short-term use only. These guidelines are often neglected in primary care practice (19, 20). Despite evolving trends in the pharmacological treatment of insomnia (21), there is a continued gap between efficacy research and the clinical practice of the management of chronic insomnia (18). This could be because the current state of research prevents an evidence-based consensus regarding the safety and efficacy of the long-term management of insomnia.

The Maintenance Treatment of Depression

Historically, the management of depression has been focused on treating acute episodes only. However, over the past two decades, several independently conducted studies clearly established that depression has a potentially chronic and relapsing course that can seriously affect lives (22–30). Recurrence rates after one, two, and three prior episodes of depression have been shown to be 50%, 70%, and 90%, respectively (22, 31). The subsequent episodes often occur sooner and spontaneously, last longer, and are more severe and less responsive to treatment (22, 32). Furthermore, Maj and associates (33) have demonstrated that early discontinuation of antidepressant therapy is associated with a 25% relapse rate within 2 months, even among patients who do not have chronic depression (33). Controlled studies of maintenance treatment in depression (23, 24, 34–36) support the efficacy of such treatment for up to 5 years. In addition, studies documenting poorer prophylaxis with lower "maintenance" doses (37–39) provide justification for the argument that "the dose that gets you better keeps you better."

As a result of these studies, a consensus started to develop regarding the need to have some patients take a full dose of antidepressant therapy for an extended time (and even for the rest of their lives). The availability of newer, safer medications, such as the selective serotonin reuptake inhibitors (SSRIs), also made it easier to continue antidepressant medication beyond the stabilization of

acute episodes of depression. However, there are at least two reasons to call for caution in recommending life long maintenance therapy in depression. First, there is a paucity of data regarding the safety of these newer agents across extended courses of prophylactic treatment. Their efficacy and apparent short-term safety has led us to use these medications in children and adolescents (40, 41), even though we do not (and cannot) know what happens to patients after taking these medications for 30–40 years. Second, the protection offered by maintenance treatments does not seem to be absolute. For example, a literature review of maintenance treatment in 1998 suggested that patients with depression could have relapse rates as high as 33% (a range of 9%–33% in different studies), despite full-dose maintenance therapy (42). A more recent review of the literature noted an average relapse rate of 15% in select studies of the maintenance treatment of depression (43). The so-called "poop-out" effect of SSRIs continues to be an important, albeit unproven, clinical concern.

However, concerns regarding the safety and efficacy of the maintenance treatment of depression need to be weighed against the sequelae of untreated depression. Apart from immeasurable suffering inflicted on patients and their loved ones, a growing body of evidence points to the effect of depression on the hippocampus and the functioning of the hypothalamic-pituitary-adrenal axis (44–46). Furthermore, recent evidence suggests that depression may decrease neurogenesis in the hippocampus (47). Another line of research points to depression putting patients at risk for type-2 diabetes (48) and cardiovascular diseases (49, 50). As stated earlier, there is also a danger of untreated depression progressing to a more severe, difficult-to-treat form of illness.

In light of these data and considerations, continuation of antidepressant therapy for 4–9 months immediately after acute treatment response has been widely recommended (51, 52). Although largely based on studies of tricyclic antidepressants, these recommendations appear pertinent to the SSRIs (35, 37, 38, 53, 54). There is also broad agreement regarding the indications for extended or indefinite maintenance treatment for depression (52, 55).

One longitudinal study has suggested that more than 50% of the cause of onset of depression can be described as exacerbations of preexisting subsyndromal states (56). This led Klerman and Weissman (57) to conclude, "Major depression does not usually just come 'out of the blue,' but represents the end product of a process that has been percolating along." This prodromal period may be as long as 8–10 years (58) and offers an opportunity to develop preventative interventions aimed at lowering the risk of the full clinical syndrome.

Like onset, the recovery from depression is gradual, with a large number of patients continuing to have residual symptoms at follow-up (22, 59). The residual symptoms are quite similar in nature to the prodromal symptoms (59) and, like prodromal symptoms, predict relapse in depression (60–62). Thus, the longitudinal course of depression seems to be that of a dynamic shift in the severity of the symptoms over time. For example, in a 12-year follow-up of 431 patients enrolled in a multicenter study, subsyndromal symptoms alternated with more severe ones over time (63). Furthermore, separate studies have demonstrated that treatment of the subsyndromal symptoms may prevent or arrest development of more severe symptoms or prevent relapse (64, 65).

The Management of Insomnia

Since the early 1970s, benzodiazepines have been the mainstay of the treatment of insomnia. There is little debate regarding the short-term efficacy of benzodiazepines in treating insomnia (66–69). However, there are no well-controlled objective data (employing polysomnograms) supporting the long-term use of benzodiazepines (66). It is possible that the objective benefits of nightly benzodiazepine therapy wane during extended treatment, although the patient's subjective (perceived) sense of benefit persists. Because of the lack of objective prospective data, there is considerable debate in the literature regarding the long-term use of benzodiazepines (70, 71).

Both sides of the debate make compelling arguments. Opponents of long-term benzodiazepine use cite evidence of the development of tolerance (72–75), rebound insomnia (76, 77), cognitive deficits (78–80), and increased risks for falls (81) and motor vehicle accidents (82). Most of the criticism seems to stem from the addictive potential of benzodiazepines. However, some argue that the presence of tolerance and withdrawal symptoms and the absence of loss of function do not constitute addiction by its strict definition. Moreover, even the extent of tolerance and rebound insomnia with benzodiazepines has been questioned. For example, Balter and Uhlenhuth (83) have shown that the liability for abuse of benzodiazepines is generally low. Similarly, Allen and colleagues (84) have demonstrated evidence of subjective benefit without tolerance or rebound insomnia for two different benzodiazepines (midazolam and temazepam) after use for 1 to 3 months.

The proponents of long-term use of benzodiazepines point out that there is no evidence of brain abnormalities on computed tomography scans with long-term benzodiazepine use (85). They also cite other studies that minimize the risks of benzodiazepines. For instance, the evidence of continued cognitive impairment despite discontinuation of benzodiazepine use in the study by Tata and associates (80) is contradicted by other studies that show that cognitive dysfunction associated with benzodiazepine use is reversible upon discontinuation (86, 87). Similarly, daytime sedation and hangover-type complaints with the use of benzodiazepines seem to improve with continued use (88, 89). Shorter-acting benzodiazepines are

even less likely to have any significant daytime sedation (89). In fact, it is even argued that hypnotic use improves alertness in patients with insomnia since untreated insomniacs often report hangover-type symptoms (83, 90). Furthermore, evidence of higher rates of falls in those taking benzodiazepines (81) is countered by evidence of higher rates of falls in those with untreated insomnia (91). Similarly, a review of the literature (70) has pointed out the limitations of the study linking benzodiazepine use with increased mortality rates (92).

The apparent contradictory results of various studies regarding the risks of benzodiazepine use stem from different research design and study populations. Most of these studies employed cross-sectional rather than longitudinal designs. The use of different diagnostic criteria for insomnia in various studies may also explain the discrepancy in the results. A complete risk-benefit analysis is also prevented by the fact that most of the studies have compared patients taking benzodiazepines with healthy comparison subjects rather than with untreated insomniacs with comparable severity and comorbidity. Similarly, studies of mortality rates in untreated insomniacs (93, 94) have not rigorously controlled for the duration of insomnia.

There have been a number of attempts to evolve a consensus on the use of benzodiazepines. The Institute of Medicine's report titled "Sleeping Pills, Insomnia, and Medical Practice" (95) noted that benzodiazepines start to lose their sedative effects from the first month onward. The National Institute of Health Consensus Conference on Drugs and Insomnia recommended limiting the use of sedative/hypnotics to 4–6 weeks, noting concern about the potential for misuse, dependency, withdrawal, and rebound insomnia (96). Similarly, APA's Task Force on Benzodiazepine Dependence, Toxicity, and Abuse (97) recommended against longer-term nightly use of a benzodiazepine and considered this to be especially hazardous for the elderly. Nevertheless, the task force noted that some elderly patients can sleep only with the assistance of a hypnotic and that the ongoing use of hypnotics in such patients may be warranted with "close supervision." However, none of these consensus statements was based on sufficient empirical research.

The benzodiazepines were deemed the safest, most effective medications for the treatment of insomnia for more than 20 years. The goal of decreasing the abuse potential of the benzodiazepines led to the search for more selective drugs. At this time, we do not know the extent to which this goal has been achieved with the development of zolpidem and zaleplon. There is some evidence that both zolpidem and zaleplon have comparable efficacy to benzodiazepines (98, 99). Of the two, there is more data regarding the use of zolpidem. A meta-analysis of the subjective measures of sleep in patients with chronic insomnia demonstrated reliable improvement with the use of zolpidem (66). However, a meta-analysis of sleep laboratory studies showed evidence of some tolerance and rebound insomnia with zolpidem use (68). The authors found inadequate data to comment on tolerance and rebound insomnia regarding zaleplon. All of the well-controlled treatment studies of zolpidem and zaleplon were limited to the first 5 weeks of use. For that matter, as stated earlier, there are no well-controlled data from sleep laboratory studies supporting the long-term efficacy of benzodiazepines. Agencies could be reluctant to fund such studies. There is also a paucity of well-controlled sleep laboratory data regarding other commonly used sleep aids, such as melatonin, valerian, diphenhydramine, and trazodone (100).

A number of behaviorally based interventions, such as stimulus control, progressive muscle relaxation, paradoxical intention, sleep restriction, biofeedback, and multifaceted cognitive behavioral therapy, have also been developed for the treatment of insomnia. Two meta-analyses (101, 102) as well as qualitative reviews and practice parameters (103, 104) have concluded that these treatments are efficacious. A more recent meta-analysis concluded that behavioral and pharmacological treatments are equally efficacious in the short-term treatment of insomnia and that one outcome, sleep latency, showed a significant advantage for behavioral treatment (69). Several recent well-controlled clinical trials have further demonstrated the efficacy of behaviorally based insomnia treatments (105, 106). Furthermore, such treatments appear to have durable effects, with treatment gains being maintained for up to 24 months.

Few studies have directly compared the relative efficacy of behavioral and pharmacological treatments, either singly, in combination, or as sequential treatments. Limited data suggest that the acute efficacy of behavioral and pharmacological treatments are equivalent, whereas sustained efficacy may favor behavioral interventions (105). However, no study has directly compared behavioral and pharmacologic interventions in a true maintenance therapy design. Therefore, further work is needed to define the appropriate roles of behavioral and pharmacological treatments, either singly or in combination, for both acute and maintenance treatment of chronic insomnia.

Summary

Longitudinal and controlled clinical trials, of the types that established maintenance treatment in depression, are needed to optimize the treatment of insomnia. These trials will have to evaluate the effects of the treatment of insomnia, as well as examine the effects of untreated insomnia. Selective agents (zolpidem, zaleplon), over-the-counter agents (e.g., diphenhydramine), "natural" products (such as valerian and melatonin), antidepressant agents used "off label" as sleep aids (e.g., trazodone and amitriptyline), combined therapies, and sequential treatments also need to be evaluated systematically. Outcome measures, such as the patients' sense of well-being, functional performance,

and the cost of treating versus not treating, need to be included. Only then can the patients and their clinicians make truly informed treatment decisions.

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