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Does Acute Treatment with Sedatives/Hypnotics for Anxiety in Depressed Patients Affect Suicide Risk? A Literature Review

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Background. *Anxiety (among several other symptoms) has been identified in one prospective study as associated with suicide risk in depressed patients early in treatment. It has been suggested that treatment of anxiety in depression with sedative/hypnotic agents, especially benzodiazepines, in the first several weeks may decrease suicide risk. Sedative/hypnotic agents also have depressant and disinhibitory properties which might increase suicide risk, however. This review addresses the potential benefits and risks with regard to suicide of using sedative/hypnotics as an early adjunct to antidepressant treatment in anxious depressed patients.*

Methods. *Pertinent medical literature was reviewed using Medline/PubMed search as well as bibliographies from related publications. Reports in English from 1958 to 2006 were included.*

Results. *The review did not reveal any evidence that using sedative/hypnotics as an early adjunct to antidepressant treatment of anxious depressed patients decreases their suicide risk. There is considerable evidence that sedative/hypnotics produce depressant and/or disinhibitory effects in a small proportion (perhaps 5%) of people who take them. However, there is no clear evidence that their brief use early in depression increases suicide risk. Toxicological data of suicides indicate that a majority of people who commit suicide are under the influence of sedative/hypnotic chemicals (including alcohol) at the time.*

Conclusions. *The authors conclude that the question of whether sedative/hypnotics may prevent or provoke suicide in anxious depressed patients cannot be answered definitively with the available information. They believe the potential risks of prescribing sedative/hypnotics for depressed patients who may be suicidal are serious. They suggest that alternatives to sedative/hypnotics should be used if early adjunctive treatment for anxiety in depressed patients is thought to be indicated.*

Keywords Suicide, Anxiety, Sedatives, Hypnotics, Disinhibition, Depression

INTRODUCTION

In the past several years, much attention has been given to the debate over whether antidepressant medications prevent or provoke suicides (1). Other classes of medications often used in the treatment of depressed people have received comparatively little attention in relation to suicide risk.

From antiquity, people have used ethyl alcohol to soothe depressive symptoms, particularly the accompanying anxiety and insomnia. The 20th century saw the development of a number of unique chemical compounds demonstrating alcohol-like effects, which were called sedatives (for reduction of waking anxiety) and hypnotics (for induction and maintenance of sleep) (Table 1). Barbituric acid derivatives, introduced over 100 years ago, were prescribed by physicians for these purposes.

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Table 1 Abusable Sedative And Hypnotic Medications

Barbiturates
Benzodiazepines
Chloral hydrate
Ethchlorvynol
Glutethimide
Meprobamate
Methaqualone
Methprylon
Paraldehyde
Tybamate

A number of other chemicals followed barbiturates. The introduction of chlordiazepoxide in 1959 was followed by the release of many other benzodiazepines. While other sedative/hypnotics (S/Hs) remain available for prescription, the benzodiazepines have assumed the lion's share of today's S/H market for the treatment of anxiety.

S/Hs are of particular interest regarding the treatment of depression for several reasons. First, anxiety and insomnia are common symptoms of depression (2). Second, one study suggests that anxiety and panic attacks may be, among several others, significant early predictors for suicide in depressed people (3). These issues suggest a possibly life-saving role for giving specific attention to anxiety early in treatment of depressed patients.

Certainly, S/Hs are highly effective for the acute and chronic relief of anxiety. The risk of dependence with regular use of these chemicals is well documented, however. All the S/Hs used for daytime anxiety are recommended for short-term use only. The rationale is that physiological dependence may take only a few weeks to develop. In spite of this, short-term prescription of S/Hs may not always be the case in clinical practice. A study of depressed patients (n = 128,029) treated in 129 Veteran Affairs facilities in 2001 examined the use of benzodiazepines (4). Among the patients with depression, 89% filled an antidepressant prescription and 36% filled a benzodiazepine prescription. Among those depressed patients who filled a benzodiazepine prescription, 78% received a ≥ 90-day supply and 61% received a ≥ 180-day supply. There was significant variation among centers and areas of the country. Nonetheless, the authors concluded that, in this setting, depressed patients ". . . commonly receive long-term treatment with benzodiazepines in combination with antidepressant, a pattern of use that is inconsistent with guideline recommendations."

There are also other specific risks to weigh when considering short-term S/Hs treatment of anxiety associated with depression. First, S/Hs, like alcohol, are central nervous system (CNS) depressants, not only physiologically (e.g., respiration) but also mentally (e.g., mood) (5). A community survey, which was funded by the National Institute of Mental Health, found that people who used "minor tranquilizers and sedatives" had significantly higher depression scores than those who did not (6).

Second, S/Hs are also intoxicants with disinhibiting properties (5). A number of toxicological studies of post-mortem alcohol detection in suicides have found a consistent range of 30–40% (7–15). More comprehensive toxicological studies have found intoxicating abusable substances (mainly S/Hs) in a majority of suicides (16–19). It is difficult, if not impossible, to ascertain the contribution of acute intoxication to any individual suicide. Nonetheless, the frequency with which intoxicants are found among suicides suggests an important role.

For this report, our goal was to critically examine evidence regarding the use of S/Hs in the management of acute anxiety in depressed patients. We specifically focused on a risk-benefit analysis of the effect of these substances related to suicide.

METHODS

We reviewed pertinent medical literature regarding the issues outlined above. We included reports in English from 1958 to January 2006 using PubMed search terms: ("benzodiazepines"[MeSH Terms] OR benzodiazepines [Text Word]) and ("suicide"[MeSH Terms] OR suicide[Text Word]). This search resulted in 593 papers.

We also searched using the terms: ("hypnotics and sedatives"[TIAB] NOT Medline[SB]) or "hypnotics and sedatives" [MeSH Terms] or "hypnotics and sedatives"[Pharmacological Action] or hypnotics[Text Word]) and ("suicide"[MeSH Terms] OR suicide[Text Word]). This resulted in 848 papers.

We also searched the bibliographies and references from these and related publications.

We selected the relevant papers from these searches and used the papers that included suicides rather than suicidal ideation or attempts whenever available. There was overlap between the above searches as can be expected.

DEFINITIONS

The definitions of various disorders in the depressive spectrum have varied through the years. For the purpose of this report, we will define depression in a simple, inclusive way, characterized by a pathological low mood together with other persistent psychic and somatic symptoms (20). The presentation does not include unhappiness that is construed to be a normal response to a stressor (e.g., bereavement). Similarly, we include the commonly accepted signs and symptoms of anxiety rather than referring to specific anxiety disorders. We include anxiety and panic attacks as a symptom(s) rather than a discrete disorder.

Included in the category of S/Hs are those chemicals with abusable potential whose primary effects are depression of the CNS as defined in a standard pharmacology textbook (5) and DSM-IV-TR (2) (Table 1). Although many of these medications are, obviously, used as anxiolytics (or anti-anxiety/panic medications), we intentionally avoid using the term anxiolytic

because it might be confused with medications such as buspirone and antidepressants that may have anxiolytic action without depressant properties.

RESULTS

Potential Advantages of Treating Anxiety in Depression with Sedative-Hypnotics

Antidepressant Effect

There are a number of published studies comparing an antidepressant to a benzodiazepine with or without placebo control. We found 17 studies showing equal antidepressant efficacy between antidepressants and benzodiazepines (21–37). We also found 18 studies in which benzodiazepines had inferior antidepressant efficacy to antidepressants (38–55). All but one of these 36 studies were short-term trials (8 weeks or less). The only longer study (16 weeks followed by a maintenance phase for 12 months) was a double-blind randomized trial comparing diazepam, imipramine, or placebo in "neurotic depression." The investigators found "significant therapeutic advantage of imipramine over both diazepam and placebo" as well as "continued advantage for treatment with imipramine" (55).

This is not surprising given that anxiety symptoms are a common occurrence in depressive disorders (and vice versa). The Hamilton Rating Scale for Depression (HAM-D), which is commonly used in these trials, contains many items that are not exclusive to depression (52). For instance, items like somatic and psychic anxiety, insomnia, agitation, impairment in work and interests, hypochondriasis, depersonalization, derealization, obsessions, and compulsions may also be symptoms of anxiety. Improvement in these symptoms by using S/Hs could substantially lower the HAM-D scale score without changing the core depressive symptoms or the morbidity of depression. Perhaps that explains the perplexing findings from two pooled placebo-controlled trials by the manufacturer of clonazepam. Depression was reported by 7% of patients taking clonazepam (leading to discontinuation in 4%) versus 1% of patients taking placebo. In spite of that, these very patients taking clonazepam showed favorable improvement on total HAM-D scores versus placebo patients (53).

In summary, it seems likely to us that early reports suggesting antidepressant effect of some benzodiazepines reflected some methodological flaws including the short treatment periods and the use of rating methods that assessed anxiety as much as depressive symptoms and signs. Moreover, as far as we can tell, long-term antidepressant effects of S/Hs have never been demonstrated in a controlled study.

Antidepressant Augmentation

More recently, attention has been given to the initial augmentation of selective serotonin reuptake inhibitor antidepressants (SSRIs) with benzodiazepines. Three studies published by the same group, Summit Research Network (54–56), have suggested that the short-term use of benzodiazepines in combination with SSRIs ". . . may reduce suffering during early SSRI treatment, may partially suppress SSRI side effects, may increase compliance. . . " (54). These studies were conducted for only a few weeks. This effect would be consistent with the earlier findings of a possible early antidepressant effectiveness of S/Hs. We cannot conclude from these studies, however, that S/Hs have a favorable effect on alleviation of depression in the long-term. Also, no data related to suicide risk are reported in these papers.

Anti-Suicide Effect

In a study of 954 patients with major affective disorder, Fawcett and colleagues found that six factors were associated with the 13 suicides that occurred within one year of entering the study: panic attacks, psychic anxiety, diminished concentration, global insomnia, alcohol abuse, and anhedonia (3). The factors that were associated with the 19 suicides occurring between years 2–10 were hopelessness, suicidal ideation, and history of previous suicide attempts. They also found panic attacks were present in 62% of those who committed suicide compared to 28% who did not commit suicide. The study was prospective, but it was neither controlled nor randomized. Patients were treated in the community by their own physicians, but follow-up evaluations were monitored by the research groups. In a subsequent review, the statement was made that "Clinical experience suggests that suicidal risk can be reduced by treating high-risk features such as panic, anxiety, and agitation aggressively with benzodiazepines or other anxiolytic agents" (57). This statement was not supported by literature references or new data, however. This also seems contradictory to the data from this very study indicating that alcohol use is also a risk factor for suicide.

The authors of the Summit Research Network studies cited above have also suggested that the short-term use of benzodiazepines in combination with selective serotonin reuptake inhibitor could "possibly reduce the risk of suicide" (54). The effect on suicide was not studied, however. Therefore, we also cannot conclude from these reports that S/Hs have a favorable effect on preventing suicide.

In summary, we found no evidence to support a conclusion that S/Hs have a suicide preventive effect among depressed patients. Only controlled clinical investigations, albeit extraordinarily difficult to perform, would be able to answer this question definitively.

Potential Disadvantages of Treating Anxiety in Depression with Sedative-Hypnotics

Depressant Effect

There is considerable evidence demonstrating that depression is an effect of S/Hs in some people. Depressive symptoms

have been described in association with barbiturate treatment of children with seizure disorders (58, 59, 60). There is much more information available concerning benzodiazepines, however.

Perhaps the first case suggesting a depressant effect ("depression with suicidal tendency") of benzodiazepines was reported by Rao from a series of 8 patients being treated with diazepam for obsessive compulsive disorder (61). Kraft et al. reported in 1965 that 2 of 130 children being treated with chlordiazepoxide for a variety of disorders were withdrawn from the study due to depression (62). In 1966, Gundlach et al. reported that 7 schizophrenic patients on diazepam vs. two on placebo developed "suicidal impulses and thoughts" (63). Also that year, McDowall et al. reported that a patient in a trial comparing diazepam to amylobarbitone dropped out while on diazepam because "it was depressing" (64). In 1968, Ryan et al. also described the development of "suicidal thoughts and tendencies" in 7 patients being treated with diazepam (65). In 1972, Hall et al. described 6 patients who developed depression, suicidal thoughts, tremors, and apprehension after a few days of initiation of diazepam (66). Lydiard et al. reported that, in an open study of 46 panic disorder patients who were receiving 3–10 mg/day of alprazolam, 33% developed symptoms consistent with DSM-III criteria for major depression despite remission of their panic attacks (67). Cohen et al. conducted a review of 177 patients treated with clonazepam and found that 10 (5.7%) developed treatment emergent depression (68). In another study of alprazolam for panic disorder, only 1 of 263 subjects "experienced an episode of major depression after 6 weeks of alprazolam" (69). According to O'sullivan et al., "troublesome depression" appeared in 6 of 73 (8%) of subjects taking alprazolam vs. none of the 71 placebo subjects in a study of agoraphobia with panic disorder (70).

In a survey of family practitioners in England, Edwards et al. found that depression and drowsiness were the most commonly reported "events" among patients being treated with alprazolam (11.5 per 1000 patients) (71). Only 49% of the originally selected sample returned useful data, however. The authors concluded that the finding of depression was ". . . more likely to be due to the underlying illness than to alprazolam." It is not clear to us, however, how such a conclusion follows from the data that were collected.

Moreover, worsening of depression has been observed and documented in short-term studies by manufacturers of clonazepam (53), diazepam (53), clorazepate (53), flurazepam (53), lorazepam (72), and phenobarbital (72).

In summary, it appears that treatment emergent depression occurs in a small but regular proportion, perhaps 5–10%, of people treated with S/Hs (especially benzodiazepines). Debate continues as to whether or not this may be a function of the disorders being treated rather than a medication effect. We believe the placebo controlled data supports the conclusion of medication effect. Either way, however, the phenomenon is important to recognize in light of the known connection between depression and suicide (1).

Disinhibition

Some case reports and case series from uncontrolled treatment settings also point to an infrequent but serious behavioral disinhibiting effect (called "paradoxical" by some) associated with several benzodiazepines. These include reports of increased anxiety, rage, hostility, violence, suicidality, and sexual disinhibition in patients being treated for a variety of psychiatric disturbances (Table 2). No actual suicides are included in these reports, however. There have also been a number of reports of similar behavioral disinhibition associated with use of intravenous benzodiazepines, particularly midazolam, for anesthesia (73–86). These reactions are short lived and generally reversible with the benzodiazepine antagonist,

Table 2 Case Reports and Case Series of Disinhibition with Benzodiazepines

Author/Year	N	Symptoms/Signs	Drug
Boyle et al., 1961 (165)	1 of 25 patients	"increase his aggressiveness"	Chlordiazepoxide
Feldman, 1962 (166)	"some instances" of 87	"overt acts of violence"	Diazepam
Kraft et al., 1965 (62)	6	"rage reaction"—1; "loss of control"—5	Chlordiazepoxide
Zucker, 1972 (167)	2	"disrobed in public"; "severe altercation with her husband"	Oxazepam
Lion et al., 1975 (168)	2	Attacked sister with knife, destroyed furniture	Clorazepate
		Attacked wife	Diazepam
Goldney, 1977 (169)	1	"Behavioral disinhibition"	Lorazepam
Zisook et al., 1977 (170)	1	Attacked superior officer with knife	Diazepam
Gardos, 1980 (171)	1	Aggression, hostility, and disinhibition	Diazepam
Rosenbaum et al., 1984 (172)	8(of 80 patients)	"hostility"	Alprazolam
Strahan et al., 1985 (173)	3	"Behavioral disinhibition"	Alprazolam
Binder, 1987 (174)	3	"Behavioral disinhibition"	Clonazepam
Kubacki, 1987 (175)	2	"Sexual disinhibition"	Clonazepam
Marrosu et al., 1987 (176)	7	"unsocialized aggressive behavior and explosive aggression"	Diazepam
Marchevsky et al., 1988 (177)	1	"Behavioral disinhibition"	Clonazepam
Noyes et al., 1988 (69)	1(of 263 subjects)	"Aggressive or violent behavior"	Alprazolam
Fava et al., 1991 (178)	1	"Sexual disinhibition"	Clonazepam

flumazenil. The anesthesia reactions indicate to us that the disinhibition is most likely a direct effect of the drug rather than an epiphenomenon associated with psychiatric disorder. Again, no suicides are reported in this situation.

The randomized placebo controlled study of panic disorder previously cited (see above) compared 73 patients taking alprazolam to 71 taking placebo (70). "Serious side-effects" of "disinhibition" ($n=3$) and "aggressive outbursts" ($n=2$) occurred in 5 of 73 patients taking alprazolam while there were none in the placebo group. A double-blind randomized crossover pilot study of 15 children was designed to study the benefit of clonazepam use as an anxiolytic in children (87). During the clonazepam phase, 2 subjects dropped out due to ". . . serious disinhibition with marked irritability, tantrums, and aggressivity (one attempted self-injury with a rope around his neck)." No suicides occurred in either study.

Several studies have attempted to explore the nature of benzodiazepine-induced disinhibition in normal subjects using psychological testing paradigms (88–92). These experiments involved relatively small numbers of subjects (10 or less per treatment condition) for relatively short periods of time. Some disinhibitory effects were generally found in the test results with the drug. The differences were not always statistically significant or clinically pronounced. No episodes of pronounced behavioral disinhibition such as noted in the clinical reports were described in these experiments. These studies have engendered some discussion as to whether the disinhibitory effect may be due either to increased levels of actual aggression or to decreased (or delayed) inhibition of natural aggressive tendencies: "A number of theories postulate that behavior is governed by two distinct systems: one that activates behavior and one that inhibits behavior. . . . The relative strength of each system is generally assumed to determine behavior control" (91). Edwards et al. proposed a simpler explanation: "A better terminology would seem to be that the benzodiazepines cause a degree of disinhibition or aggressive response which in few cases may be extreme" (93, 94).

In summary, it appears that serious disinhibitory phenomena, like depression, occur in approximately 5–10% of people prescribed benzodiazepines. As far as we are aware, there is no reliable method of predicting which patients are at risk for the disinhibiting effect of S/Hs (95). None of the reports cited in this section contain any suicides. On the other hand, the high rate of detection of intoxicating abusable substances among suicides (7–19) makes this a serious practical consideration for suicide prevention.

Potential Alternatives to Sedative-Hypnotics for Treating Anxiety in Depression

We could not find evidence supporting the contention that early separate treatment of anxiety in depression in addition to antidepressants will prevent suicides. There is also really no evidence to the contrary. Consequently, the decision to prescribe separate treatment for the anxiety must be made in individual circumstances. The potential risks of using S/Hs for that purpose, though, suggest it may be important to consider alternatives to S/Hs.

Hydroxyzine (as the hydrochloride and pamoate salts) has shown efficacy in treating anxiety symptoms in both acute (96–98) and in longer term clinical situations (99–104), including several placebo-controlled trials (105–107). It has also compared favorably to benzodiazepines (97, 98, 103, 107) and buspirone (106). Dosage recommended by the manufacturer for treatment of anxiety is 50–100 mg four times a day. A frequent complaint about hydroxyzine is drowsiness, probably related to antihistamine sensitivity. The study by Darcis et al., however, found that the difference in reports of drowsiness between hydroxyzine (28%) and placebo (14%) was not statistically significant (105). Lader and Scotto reported somnolence in 9.9% of the hydroxyzine patients compared to 4.9% with buspirone and none with placebo (106). They noted the somnolence was transient ". . . and had largely disappeared by day 10 except for one patient." In our clinical experience, the drowsiness does limit initial patient acceptability by those who experience it, albeit the minority.

There have been numerous reports in recent years on the use of several of the newer anticonvulsant and antipsychotic medications for treating anxiety in a variety of disorders and clinical situations including augmentation of antidepressants. These include divalproex (108–111), tiagabine (112–116), gabapentin (117, 118), pregabalin (119–125), quetiapine (126–129), olanzapine (130–135), risperidone (129, 136, 138), ziprasidone (139), and aripiprazole (140, 141). Until more formally presented data are available, though, we cannot make any recommendations in this regard.

Our experience and personal contacts with other psychiatrists suggest that small doses of the newer antipsychotics in particular may be gaining some off-label use for this purpose. The doses used in the studies of alternative medications for the treatment of anxiety are shown in Table 3. If any of these medications did prove to have anxiolytic efficacy equivalent to S/Hs, there might be some advantages to their use for that purpose. The lack of physical dependence would be a major advantage. Some of these medications appear to have a favorable effect on depression (142–151). In fact, two of these now have approved FDA indication for adjunctive treatment of major depressive disorder (aripiprazole) and bipolar depression (quetiapine). There is also some evidence suggesting a possible suicide preventive effect of some newer antipsychotics when treating schizophrenia (152–156). Finally, the short-term and low-dose use of these medications would likely minimize their metabolic and other risks. It seems to us that controlled trials to compare alternative medications to S/Hs for treating anxiety in depression would be well justified by the available information.

It is also worth noting that some forms of psychotherapy (e.g., cognitive-behavioral, relaxation) alone and in addition to antidepressants have been shown in some studies to be equally

Table 3 Doses Used in Studies of Alternative Medications for the Short-Term Treatment of Anxiety

Medication*	Study	N	Dose Used in the Study	Type of Study/Duration
Divalproex	Primeau et al., 1990 (109)	10	500 mg/day–2250 mg/day as tolerated	Open-label/7-week
	Lum et al., 1991 (110)	12	250 mg/day	Double blind placebo-controlled crossover/6-week
	Woodman and Noyes, 1994 (111)	12	Started with 500 mg/day and increased according to response and side effects	Open-label trial/6-week
Gabapentin	Chouinard et al., 1998 (117)	18	Main beneficial effects at 200–1800 mg daily (min 100 and max 4400 mg/day, usually in divided doses)	Naturalistic study
	Pande et al., 2000 (118) *N*=103		600–3600 mg/day	Randomized, double-blind, placebo-controlled parallel-group/8-week
Pregabalin	Feltner et al., 2003 (119)	271	50 mg t.i.d. or 200 mg t.i.d.	Double-blind, fixed-dose, parallel-group, placebo- and active-controlled multicenter study/4-week
	Pande et al., 2003 (120)	276	150 mg/day or 600 mg/day	Double-blind, randomized placebo-controlled study/6-week
	Rickels et al., 2005 (121)	454	300 mg/day, 450 mg/day, or 600 mg/day	Double-blind, placebo-controlled trial/4-week
	Pohl et al., 2005 (122)	344	100 mg b.i.d., 200 mg b.i.d., or 150 mg t.i.d.	Double-blind randomized trial/6-week
	Montgomery et al., 2006 (124)	421	400–600 mg/day	Multicenter, randomized, double-blind, placebo-controlled trial/6-week
	Stein, 2007 (125)	426	400 mg/day or 600 mg/day	Multicenter, randomized, double-blind, placebo-controlled trial/6-week
Tiagabine	Rosenthal, 2003 (112)	40	4 mg/day during week 1, between week 2 and 6 dose was individually increased (maximum increase of 4 mg/week) for optimal response of 16 mg/day	Randomized, open-label clinical trial/10-week
	Crane, 2003 (113)	10	2 mg/day for 1 week then increased if no response to initial dose up to 8 mg/day	Open-label/3-month
	Schwartz et al., 2005 (114)	18	4 mg/day for 2 days and increased to 8 mg/day for 10 days. Dose was then adjusted according to efficacy/tolerability in increments of 2 mg every 3 days up to a maximum of 20 mg/day	Open-label study/8-week
	Pollack et al., 2005 (115)	260	4 mg/day then flexibly dosed twice a day and increased to a maximum of 16 mg/day	Randomized, double–blind, multicenter, placebo-controlled trial/8-week
	Carpenter et al., 2006 (116)	19	Started at 4 mg/day and titrated to optimum response as tolerated to a max of 20 mg/day	Open-label/8-week
Aripiprazole	Worthington et al., 2005 (140)	17	15 mg/day and 30 mg/day	Retrospective case review
	Adson et al., 2005 (141)	10	Starting at 5 mg/day then increased by 5 mg/day at weekly increments to a maximum of 20 mg/day	Open-label study/9-week

Olanzapine	Tollefson and Sanger, 1999 (130)	1948	5–20 mg/day	Post–hoc, multi-national, randomized, double-blind trial
	Mintzer et al., 2001 (131)	206	5 mg/day	A post-hoc analysis of double–blind, randomized study/6-week
	Tohen et al., 2003 (132)	833	5–20 mg/day	Double-blind, randomized, controlled multicenter trial/8-week
	Littrell et al., 2003 (133)	24	Started at 5 mg/day during week 1, increased to 10 mg/day during week 2, and then titrated up to 20 mg/day based on clinical response	Open trial/6-month
	Hollifield et al., 2005 (134)	10	Started at 2.5 mg q.h.s., titrated as needed to a maximum of 20 mg q.h.s.	Open-label/8-week
	Pollack et al., 2006 (135)	24	2.5 mg/day for first week, 5 mg/day for second week, and then flexibly titrated in 5 mg/day increments per week up to a maximum of 20 mg/day over the next 4 weeks	Randomized, double–blind, placebo-controlled trial/6-week
Quetiapine	Adson et al., 2004 (126)	11	Started at 25 mg q.h.s., increased as needed in 25-mg increments to a maximum of 100 mg in the morning and 200 at q.h.s. (300 mg/day)	Open-label, variable-dose study/9-week
	Kasper, 2004 (127)	415	Fixed-dose quetiapine groups 75, 150, 300, 600, 750 mg/day, 450 mg/day given in two or three divided doses daily, and 50 mg/day given b.i.d.. Flexible dose group given up to a maximum of 800 mg/day	Open-label extension phases of three randomized clinical trials of quetiapine/156-week
	Galynker et al., 2005 (129)	36	Started at 25 mg q.h.s., increased by 25 mg/day to 100 mg/day and then by 50 mg/day to 300 mg/day	Case series
	Hirschfeld et al., 2006 (128)	542	600 mg/day or 300 mg/day	Randomized, placebo-controlled trial/8-week
Risperidone	Blin et al., 1996 (136)	62	4–12 mg/day	Randomized trial/4-week
	Galynker et al., 2005 (129)	36	Risperidone was started at 0.125 mg q.h.s., increased by 0.125 mg to 0.25 mg and then by 0.25 mg/day to 0.5 mg/day	Case series
	Brawman-Mintzer et al., 2005 (137)	40	0.5–1.5 mg/day	Double-blind, placebo-controlled study/5-week
	Simon et al., 2006 (138)	30	0.25–3.00 mg/day	Open-label trial/8-week
Ziprasidone	Snyderman et al., 2005 (139)	13	20–80 mg/day (started at 20 mg daily, then, depending on response and tolerability, the dose could be increased in 20-mg/week increments) b.i.d. or once-daily dosing	Open-label study/7-week

*Medications arranged alphabetically with anticonvulsants first then antipsychotics.

effective to medications for treatment of anxiety symptoms in panic and generalized anxiety disorders (94, 157–162). A study comparing relaxation therapy to diazepam in treatment of panic disorder reported that diazepam showed more change on the physiological aspect of anxiety. "The largest pre/posttreatment changes on the psychological tests and self-reported anxiety and depression occurred with relaxation, although the differences were not statistically significant" (163). We found no studies looking at early treatment of anxiety in depression with psychotherapy, however. It seems unlikely that psychotherapy would carry any risks of causing depression or disinhibition. The question then is whether or not a particular form of psychotherapy would be efficacious for the anxiety in that situation. Obviously, specific studies would have to be conducted to answer the question.

In summary, alternatives to S/Hs do exist. Hydroxyzine has been the best studied of these, but perhaps 1 in 5 people may experience bothersome drowsiness, at least in the immediate use, which may pose a problem of acceptability. Other medications may show some promise for treating anxiety and may be preferable in depressed and potentially suicidal patients. However, more formal studies to determine their place in the anxiolytic armamentarium are needed.

LIMITATIONS

In addressing the potential benefits and risks in this review, we considered the effects of S/Hs in general. It is possible that different S/Hs may have quite different effects on the CNS that may be contrary to expected effects. Likewise, there may be similar dose-related differences among the S/Hs. Moreover, some of the studies cited include patients who are taking antidepressants or other medications along with S/Hs. These patients may react differently while on more than one medication.

The available data also have the inherent limitations that they do not directly test the effect of S/Hs on suicide rate. Controlled clinical studies needed to test for a correlation between S/Hs and suicide risk, as with antidepressants, are virtually impossible to perform due to the huge number of patients needed as well as the ethical constraints of including potentially suicidal patients in such studies (164).

CONCLUSIONS

1. Diagnosis of the condition(s) responsible for the depression and anxiety should direct the primary treatment modality. This may include appropriate pharmacotherapy and/or psychotherapy.
2. There are no conclusive data indicating whether or not S/Hs protect against suicide when prescribed for depressed patients. This is true regardless of the duration of S/Hs use.
3. The propensities of S/Hs to induce depression and disinhibition are infrequent, but they are largely unpredictable. Toxicological data of suicides indicate that a majority of people who commit suicide are under the influence of sedative/hypnotic chemicals. Therefore, we believe the use of S/Hs should be avoided in these circumstances.
4. If specific medication for anxiety symptoms is felt to be important early in the treatment of depression, alternatives to S/Hs should be considered.

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