# Phenomenology and Treatment of Agitation

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Agitation is a troublesome, common symptom in major depression that can be difficult to manage. It is sometimes a side effect of antidepressant treatment and may occasionally represent a mixed bipolar episode. If agitation fails to respond to an antidepressant alone, treatment may be augmented with a benzodiazepine, a neuroleptic, or lithium. Preliminary evidence indicates that divalproex, which has been found useful for bipolar disorder and for agitation associated with Alzheimer's disease, may also be effective for agitated depression. A controlled trial is now underway.

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Agitation, defined as motor restlessness such as fidgeting and pacing associated with an inner tension, is a troublesome and relatively common symptom in up to two thirds of patients with depression and is also often observed in a variety of other psychiatric disorders including anxiety disorders, dementia, and mania. A relationship may exist with anxiety, which has frequently been linked with agitation in the literature, as well as anger in patients with severe depression. Agitation may be difficult to manage in patients with major depression, who sometimes experience the emergence of agitation as a side effect when antidepressants are initiated. Some patients require the addition of other agents such as benzodiazepines, antipsychotics, and, recently, anticonvulsants.

## PREVALENCE

The prevalence of agitation in major depression appears to vary with the severity of the depression, but not with age. While agitation has been reported to occur more often in depressed individuals 40 years or over than in those 39 years and younger,[1] Musetti et al.[2] were unable to confirm the clinical stereotype that ascribes greater agitation to patients over 65 years.

The incidence of agitation appears to be higher in severely depressed patients as opposed to those with a mild form of depression. Gibbons et al.[3] reported that agitation is one of the dimensions that defines global depression severity. My colleagues and I studied 2 samples[4,5] of patients with major depression and found a higher incidence of agitation in the more severely depressed sample. Ratings were made by using the agitation subscale of the Hamilton Rating Scale for Depression (HAM-D), which ranges from 0 (no agitation) to 1 (mild motoric restlessness) to 4 (frank pacing and irritability). One sample[4] included 58 subjects with moderate-to-marked depression, 25 inpatients and 33 outpatients, whose mean ± SD total HAM-D score was 26 ± 4. We found that 39 (67%) had some degree of agitation, and 22 (39%) had moderate-to-severe agitation (HAM-D agitation subscale score = 2–4; Table 1). Agitation was reported less frequently in a larger sample of patients (N = 84) with a wider range of severity of depression (mild to marked).[5] When the patients, whose mean ± SD HAM-D score at baseline was 23 ± 5, were assessed for the presence of agitation, only 9 (10%) were rated at 2 or higher on the HAM-D agitation subscale, although 40 other patients (48%) received a rating of 1. In all, 58% of the sample was assessed as having some degree of agitation, although symptoms were mild in most patients.

Both samples included adults between the ages of 18 and 65 years who were studied under drug-free conditions. Because older agitated patients generally have more difficulty than younger patients in going without a sedative agent, this incidence is probably conservative. Still, the data suggest that agitation is relatively common in major depression.

## RELATIONSHIP BETWEEN AGITATION AND ANXIETY

While some investigators have found that agitation and anxiety occur independently in depressed patients,[6] others have reported a relationship between the 2 symptoms.[7] Spearman rank order correlations from the 2 studies discussed above[4,5] suggested that agitation and anxiety are independent in depression.[6] While total HAM-D scores cor-

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Table 1. Severity of Agitation in Major Depression[a]

| | Study 1[b] (N = 58) | | Study 2[c] (N = 84) | |
|---|---|---|---|---|
| Agitation Score | N | % | N | % |
| 0 | 19 | 33 | 35 | 42 |
| 1 | 17 | 29 | 40 | 48 |
| 2 | 16 | 28 | 7 | 8 |
| 3 | 5 | 9 | 2 | 2 |
| 4 | 1 | 2 | 0 | 0 |

[a]As assessed by the agitation subscale of the Hamilton Rating Scale for Depression (0 = absence of agitation to 4 = frank pacing, irritability).
[b]Data from reference 4.
[c]Data from reference 5.

Table 2. Anxiety Symptom Ratings in 327 Patients With Primary Unipolar Depression[a]

| | Moderate Rating | | Severe Rating | |
|---|---|---|---|---|
| Symptom | N | % | N | % |
| Worrying[b] | 100 | 30.6 | 143 | 43.7 |
| Panic attacks[c] | … | … | 88 | 26.9 |
| Somatic anxiety[b] | 69 | 21.1 | 67 | 20.5 |
| Psychic anxiety[b] | 89 | 27.2 | 124 | 37.9 |

[a]Adapted from reference 7.
[b]The range of ratings was 1–6 (1 = not at all, 4 = moderate, 5 = severe, 6 = extreme); ratings of 5 or 6 were scored as severe.
[c]The range of ratings was 1–3 (1 = not present, 2 = probable, 3 = definite); ratings of 2 or 3 were scored as severe.

related significantly with the agitation scores ($p = .01$), the psychic anxiety and somatic anxiety items did not correlate with the agitation item in either sample. The agitation item identifies motoric restlessness, increased thinking, and irritability that differ from both the somatic preoccupation and bodily concern of somatic anxiety and the palpitations and sweating of psychic anxiety.

However, other studies have reported potential relationships between agitation and anxiety. Clayton et al.[7] found a high frequency of anxiety symptoms in 327 patients with unipolar depression. Worrying, for example, occurred at a moderate or severe degree in almost 75% of these patients (Table 2). Psychic anxiety, somatic anxiety, and panic attacks were also common. When the authors divided the patients into groups with high (N = 172) and low (N = 155) anxiety ratings and used a cluster analysis technique, they found that psychomotor agitation and subjective anger, as rated on the Schedule for Affective Disorders and Schizophrenia, were significantly more intense in the high-anxiety group than the low-anxiety group ($p < .001$). In many of these patients, the subjective anger occurred in combination with psychomotor agitation. The authors suggested that outcome is often poor in highly anxious patients, who are likely to exhibit symptoms of agitation. Investigators have also reported that anxiety and agitation may be associated with suicide risk.[8] Although anxiety and agitation may be associated, my colleagues and I[6] found them not to be highly correlated and to describe somewhat different clinical features.

## RECOGNITION OF AGITATION

Agitation, which can be a side effect of treatment with most antidepressants, sometimes causes patients to discontinue therapy. At one time, agitation was thought to be primarily a side effect of selective serotonin reuptake inhibitors (SSRIs) because it was observed during the early fluoxetine trials in which the 20 mg/day starting dose was pushed to 60 mg/day in 1 week. Subsequent analysis indicated that agitation is seen more often at doses of 60 mg/day or greater of fluoxetine than at lower doses.[9] Agitation that emerges during antidepressant treatment is frequently dose-dependent and may be minimized by starting patients at a low dose and titrating slowly.

Table 3. Similarities Between Agitated Major Depression and Mixed Episodes

| Similarity | Difference in Major Depression |
|---|---|
| Psychomotor agitation | Purposeless, often in early morning |
| Increased thoughts | Often time-limited at night |
| Decreased sleep | No decrease in need for sleep |
| Distractibility | Internally driven |

### Mixed Episode vs. Agitated Depression

The emergence of agitation during treatment may occasionally represent a mixed bipolar episode. In contrast to widely accepted theory, Mitchell et al.[10] suggest that agitation may be more common than psychomotor retardation in bipolar depression; thus, agitation in depression may not necessarily be a sign of emerging mania. Before a mixed episode can be diagnosed, the clinician must determine that the patient meets criteria for hypomania or mania, and symptoms in patients with agitated major depression and mixed states are sometimes similar and sometimes different (Table 3). Patients with agitated major depression, unlike those with mania, do not, by definition, demonstrate grandiosity, stated decreased need for sleep, increased talkativeness, external distractibility, increases in goal-directed activities, or interest in pleasurable activities. While psychomotor agitation is often observed in both groups, in the depressed patient, the agitation is purposeless and likely to occur predominantly in the early morning. Both groups may report decreased sleep, but patients with major depression call it insomnia and find the lack of sleep dystonic. They have trouble falling asleep and often ruminate or awaken agitated in the early morning. Both groups may appear to be distractible, but it is difficult to shift the depressed patient away from internal preoccupation with, for example, health or guilt.

Carroll[11] proposed a dimensional framework for understanding possible neurobiological and clinical differences between depression and mania. His system describes the dysregulation of several neurobiological systems—reinforcement/reward, central pain, and psychomotor reg-

Table 4. Neurobiological Systems: Dysregulation in Mania and Depression[a]

| System | Depression | Mania |
|---|---|---|
| Reinforcement/ reward | Inhibited<br>Lack of pleasure<br>Negative cognitions (internal) | Disinhibited<br>Overattention to external stimuli |
| Central pain | Usually nonaversive stimuli are distressing | Cognitive blindness to aversive stimuli<br>Denial of illness |
| Psychomotor regulation | Decreased energy<br>Decreased speech volume & quantity<br>Decreased thought processes | Increased energy<br>Increased speech volume & quantity<br>Increased thought processes |

[a]Data from reference 11.

ulation—in depression and mania (Table 4). For example, agitated depressed patients might demonstrate a depressive pattern in terms of reinforcement/reward and central pain but have features of manic-like psychomotor dysregulation. This dimensional approach should prove useful for developing new classification systems for mood disorders. Patients could be classified on the basis of the amount of psychomotor agitation as having angry depression or agitated depression, for example. Affective instability could be a classification for some depressed patients who become agitated on antidepressant treatment and who may, in fact, have an underlying bipolar diathesis but not meet the DSM-IV criteria for a mixed episode, either because they lack the requisite number of symptoms or the symptoms were not present for a sufficiently long period of time.

### Agitation vs. Akathisia

Agitation in major depression may resemble neuroleptic-induced acute akathisia. While the distinction between agitation and akathisia is often based on subjective observations, the Parker et al.[12] method of rating psychomotor disturbance in depression distinguishes between the two. Neuroleptic-induced akathisia tends to bother observers more than it does the patient. Generally, the patient with akathisia has an intense, uncomfortable butterfly-like sensation in the legs or abdomen and fidgety behaviors. Akathisia, which is generally a drug-induced state, is usually divorced from the affective state, and patients with akathisia are seldom irritable or anxious. In contrast, agitated patients, whose symptoms primarily exist at baseline, may report, "I'm jumping out of my skin. I can't sit still." They are frequently irritable and have symptoms of anxiety. Evidence of the distinction between agitation and akathisia is the fact that neuroleptics treat agitation and cause akathisia.

## TREATMENT

Although there are relatively few controlled trials of medication for agitated depression, historically the 3 major treatments when an antidepressant alone is not sufficient have been a benzodiazepine, a neuroleptic, or lithium added to an antidepressant. While these are often helpful, some patients fail to respond to these agents. Divalproex, which has been used successfully for agitation in bipolar disorder and in Alzheimer's disease,[13–16] may also be useful for agitated depression. Divalproex is generally better tolerated than lithium and has clinical advantages over benzodiazepines or neuroleptics, which carry risks for confusion and extrapyramidal reactions, particularly in the elderly. The effect of divalproex on cytochrome P450 is minimal, which lessens the risk of drug interactions. My colleagues and I[6] found divalproex to be effective in 2 patients with agitated depression.

### Case 1

Ms. A is a frail 78-year-old woman who had a 4-year history of recurrent major depression with psychotic features. The most recent episode was characterized by severe anorexia, nihilistic and somatic delusions, anhedonia, and severe agitation. She lacked a history of hypomania or mania but had made multiple suicide attempts, including throwing herself off a fourth-story balcony. Various strategies had been tried with little success. They included typical (8 mg of perphenazine b.i.d.) and atypical (6 mg of risperidone b.i.d.) neuroleptics, benzodiazepines (0.25 mg of clonazepam or alprazolam t.i.d. or 1 mg of lorazepam t.i.d.), 10 mg of buspirone t.i.d., 400 mg of meprobamate t.i.d., and 150 mg of trazodone h.s. While several series of electroconvulsive therapy (ECT) improved Ms. A's agitation and depression, the most recent ECT attempts were characterized by several complications. Pharmacotherapy was resumed with 150 mg of sertraline q.i.d., 0.25 mg of alprazolam t.i.d., and 3 mg of risperidone b.i.d. Depression and psychosis improved, but agitation and frequent verbal outbursts continued. Divalproex was initiated at 125 mg b.i.d to target the agitation. After the dose was increased to a blood divalproex level of 96 μg/mL, agitation was markedly reduced. Ms. A's verbal outbursts of anger also decreased dramatically, but she stopped taking the medication due to nausea after 4 weeks. Within 1 week, the verbal outbursts and agitation resumed.

### Case 2

Ms. B is a middle-aged, severely depressed woman who had a 4-year history of severe depression characterized by anhedonia, fatigue, insomnia, and restlessness. She lacked a clear history of mania or hypomania and her episodes did not meet criteria for a mixed state. She experienced waves of agitation lasting about 15 minutes as well as early-morning awakening. She had trouble sitting still and felt her mind was racing. Antidepressant treatment (nortriptyline, fluoxetine, desipramine, imipramine, and trazodone prescribed either alone or in combination

with lithium or benzodiazepines) increased the agitation. Ms. B was eventually started on a regimen of 225 mg/day of bupropion, which provided some relief of the depression, but the agitation and insomnia were unchanged or worse. Divalproex 750 mg/day was added and then increased to 1500 mg/day. A blood divalproex level of 90.9 µg/mL was associated with marked improvement in agitation, which has persisted for 3 years.

Divalproex has been reported to be useful for the agitation that often appears in elderly demented patients,[15,17] which led us to undertake a controlled double-blind trial of divalproex versus placebo augmentation in patients who have agitated major depression and are being treated with a selective serotonin reuptake inhibitor. A self-report rating scale, which is aimed at assessing motoric restlessness, anxiety, and irritability, is being developed for use in this trial, since many of the current instruments are aimed primarily at nursing home patients or those with brain injuries. We hope to discover whether divalproex can be helpful in treating agitation associated with depressed mood.

## CONCLUSION

Agitation is a relatively common symptom in major depression that can be difficult to manage. There may be a relationship between symptoms of agitation and anxiety in depressed patients. When antidepressants alone are insufficient to relieve agitation in depression, treatment is often augmented with a benzodiazepine, neuroleptic, or lithium. However, preliminary evidence exists for the usefulness of divalproex in agitated depression. Controlled trials are necessary to establish efficacy and determine a dosing strategy.

*Drug names*: alprazolam (Xanax), bupropion (Wellbutrin), buspirone (BuSpar), clonazepam (Klonopin), desipramine (Norpramin and others), divalproex (Depakote), fluoxetine (Prozac), lorazepam (Ativan and others), meprobamate (Equanil and others), nortriptyline (Pamelor and others), perphenazine (Trilafon), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others).

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## DISCLOSURE OF OFF-LABEL USAGE

The authors of this article have determined that, to the best of their knowledge, the following agents mentioned herein are *not* approved for treatment of agitation: divalproex, olanzapine, and reboxetine.