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A Dimensional Approach to Measuring Antidepressant Response: Implications for Agomelatine

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Current antidepressant treatments for Major Depressive Disorder (MDD) have limited efficacy and effectiveness. While measurement of response and remission is typically based on overall symptom reduction, the utilization of a dimensional approach, involving mood, cognitive and neurovegetative symptoms, may be more effective in predicting response to different antidepressant classes. In addition to these dimensions, evaluation of function is increasingly recognized as an important patient indicator of antidepressant efficacy. This paper reviews the efficacy of second generation antidepressant classes across the proposed symptom dimensions, and explores the potential benefits of agomelatine. While further research is required, agomelatine generally performed well in the mood dimension including measures of depressed mood, anxiety and anhedonia without inducing emotional blunting. Improvements in daytime alertness and clear thinking, combined with measures of subjective and objective sleep differentiate agomelatine from other currently available antidepressants, and likely contribute to favourable functional outcomes.

Keywords: Symptom Dimensions; Major Depression; Antidepressants

A Dimensional Approach to Antidepressant Outcomes

In general, the results of clinical trials and meta-analyses are based on overall reduction of depression symptoms, and demonstrate the limited efficacy and effectiveness of current antidepressants (Cipriani et al., 2010; Warden et al., 2007). Even in remitted patients, specific residual symptoms are common and contribute to poor outcomes and increased risk of relapse (Conradi, Ormel, de Jonge, 2010; Fekadu et al., 2011). For example, in a large study of patients treated with fluoxetine the most frequent residual symptoms were impairments in interest, mood, concentration, sleep, weight, and fatigue (Nierenberg et al., 1999). These symptoms fall into the same dimensions of mood, cognition, and neurovegetative symptoms that were derived from factor analyses of individual items from several depression rating scales (Korszun et al., 2004; Uher et al., 2008; Brodbeck et al., 2011).

The utility of a factor-based approach to evaluate antidepressant response (see **Table 1** Korszun et al., 2004) to different antidepressant classes has also been demonstrated (Uher et al., 2009). While there were no differences between nortriptyline and escitalopram based on either the Hamilton Rating Scale for Depression (HRSD; Hamilton 1960) or the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), there were significant differences in outcome between nortriptyline and escitalopram on each of the three symptom dimensions. Mood and cognition symptoms improved more with escitalopram while neurovegetative symptoms including sleep, showed greater improvement in the nortriptyline group (Uher et al., 2009). These findings suggest that a dimensional approach to exploring differences between antidepressants may help to personalize treatment strategies

based on symptom profile.

Each of these symptom dimensions is likely to influence social and occupational functioning which reflect patients' perceptions of favourable antidepressant outcome. For example, when patients were asked to describe their concept of remission, they identified optimism, self-confidence, emotional control, success at school, work or home, and enjoying relationships as being the most valued outcomes with antidepressant therapy (Zimmerman et al., 2006). The Sheehan Disability Scale (SDS) is a brief-three item self-report measure of satisfaction with social, family and work or school function (Sheehan et al., 1996) which has been used to compliment symptom rating scales and to provide a more comprehensive profile of treatment outcome.

Agomelatine

Agomelatine is the first melatonergic antidepressant with MT_1 and MT_2 agonist and $5\text{-}HT_{2C}$ antagonist properties (Audinot et al., 2003; Millan et al., 2003): current evidence suggests that synergy between these two mechanisms is required for antidepressant effect (Racagni et al., 2011). Agomelatine differs from standard antidepressants in its lack of direct effects on either serotonin or norepinephrine transporters (Millan et al., 2003).

The purpose of this review is to compare current second generation antidepressants and agomelatine across dimensions of mood, cognition and neurovegetative symptoms, and on functional outcome, recognizing that dimensional analyses have not been the primary focus of most trials.

Mood Dimension

The mood dimension of depression can be conceptualized to include depressed mood, anxiety and loss of pleasure or interest

Table 1.
Classification of symptom dimensions using factor analysis (Korszun et al., 2004).

Factors	Symtoms
1) Mood	Depressed mood, anhedonia, loss of hope, loss of reactivity, loss of interest, low self esteem, psychomotor retardation, loss of energy, loss of libido
2) Anxiety	General anxiety, free floating anxiety, anxious foreboding, general rating of phobias
3) Melancholia	Psychomotor agitation, pathological guilt, guilty ideas of reference, suicidality, morning worsening of depression
4) Neurovegetative	Loss of appetite, early morning waking inversely correlated with increased appetite, hypersomnia

(anhedonia). In addition, loss of reactivity (emotional blunting) has been increasingly explored in relation to SSRI treatment and may cause additional burden for patients.

Depressed Mood

Since depressed mood is a pivotal criterion for the diagnosis of a depressive episode, drug-placebo separation on this item is given particular attention in evaluating antidepressant efficacy and optimal dosing (Dunner & Dunbar, 1992; Mendels et al., 1993). Bech (2001) evaluated the single "depressed mood" item in a meta-analysis of 4 three arm trials (mirtazapine n = 182, amitriptyline n = 187, placebo n = 184) which showed that both mirtazapine and amitriptyline groups obtained an effect size that was statistically significant against placebo as early as one week after treatment. Change from baseline to endpoint on the mood item was useful in discriminating between high and low doses of paroxetine-controlled release (Trivedi et al., 2004) and in evaluating the efficacy of paroxetine in adolescent depression (Keller et al., 2001). Interestingly, achieving a combined score of zero on the mood and psychic anxiety items of the HRSD after two weeks was predictive of achieving remission during treatment with venlafaxine (Silverstone et al., 2002).

The "depressed mood" item was also assessed in a meta-analysis of placebo-controlled agomelatine trials, there was a significant mean difference between agomelatine and placebo in the total population (0.29, $p < .001$) and in the subgroup with higher baseline severity (baseline HRSD ≥ 5; 0.35, $p < .001$) (Demyttenaere, 2011).

Anxiety

Anxiety symptoms or comorbid anxiety syndromes are prevalent in depression. The rate of "anxious depression" (defined as a score ≥ 7 on the anxiety/somatization subscale of HRSD) in large samples of MDD patients is approximately 50% (Papakostas & Larsen, 2011) and 40% of depressed individuals have a comorbid anxiety disorder (Reiger et al., 1990). While definitions of anxious depression differ, there is considerable agreement that the prognosis is worse for depressed patients with high levels of anxiety following treatment with currently available antidepressants (Fava et al., 2008; Souery et al., 2007). During a large 12-week trial involving over 500 MDD patients treated with flexible dosing of fluoxetine, early symptom changes were assessed in relation to treatment outcome (Farabaugh et al., 2010). Only early changes (defined as those observed between baseline and week 1) in the "anxiety/somatization" subscale on the HRSD predicted remission.

The effect of agomelatine in anxious and non-anxious de-

pression has been compared with placebo (Loo et al., 2002) and against comparators in a recent meta-analysis (Stein & Kennedy, 2011). Compared to placebo, there was a separation of 3.43 points on the Hamilton Anxiety Rating Scale (HAM-A; Hamilton 1959) at endpoint ($p = 0.011$) and greater differences were observed when only patients with high baseline levels of anxiety (HRSD anxiety subscale ≥ 5) were included. Similarly, in the trials comparing agomelatine with either an SSRI or an SNRI, where the HAM-A was administered (Lemoine et al., 2007; Hale et al., 2010; Kasper et al., 2010) there were significant advantages in favour of agomelatine in both the total population (1.39 points, $p < .0006$) and in the subpopulation with higher baseline anxiety (1.72 points, $p = .032$) (Stein and Kennedy, 2011).

The anxiolytic effects of agomelatine have also been evaluated using the Hospital Anxiety and Depression scale (HADS; Zigmond & Snaith, 1983) in two 8-week, randomized placebo-controlled trials at fixed doses of 25 mg and 50 mg (Zajecka et al., 2010; Stahl et al., 2010). There was a statistically significant anxiolytic effect in the 50 mg agomelatine group from week 2 until endpoint ($p = 0.016$) in one trial (Zajecka et al., 2010) and in the 25 mg agomelatine group in the other trial (Stahl et al., 2011).

Anhedonia

Anhedonia, as defined by the DSM-IV-TR, is characterized by a diminished interest or pleasure in response to stimuli that were previously perceived as rewarding in a premorbid state (American Psychiatric Association, 2000). Although it is a core symptom of depression, anhedonia has not been evaluated extensively. Nevertheless, there is emerging interest in exploring the effects of different antidepressants on anhedonia, from both clinical and neurobiological perspectives (Ossewaarde et al., 2011). For example, in a comparison of atypical antipsychotics, anhedonia and social function were improved significantly more by aripiprazole than by risperidone (Liemburg et al., 2011). This preferential antidepressant effect with aripiprazole has been linked to its action on dopamine (D)-2 and serotonin (5HT) receptors (Blier & Blondeau, 2011).

The impact of different antidepressants on reward processing has also been investigated using a novel paradigm for pleasant and aversive stimuli: volunteers who received an SSRI subjectively reported and showed evidence on neuroimaging of a blunted response to liquid chocolate placed on their tongue (pleasure) and to pictures of mouldy strawberries and chocolate (aversive) after receiving the SSRI citalopram compared with those who received reboxetine (a norepinephrine reuptake inhibitor) (McCabe et al., 2010).

Greater severity of anhedonia predicted longer time to remission in a large "Treatment of Resistant Depression in Adolescents" (TORDIA) clinical trial, comparing switch options involving SSRI or venlafaxine alone or combined with CBT (McMakin et al., 2012). Results of two small proofs of concept agomelatine trials showed a significant reduction in anhedonia scores on the Snaith-Hamilton Pleasure Scale (Snaith et al., 1995) during treatment (see Di Giannantonio et al., in press).

Emotional Blunting

Among patients with SSRI-induced sexual dysfunction, 80% reported emotional blunting. They described experiences of reduced creativity, ability to cry, and care for the feelings of others (Opobroek et al., 2002). This phenomenon has subse-

quently been explored in a randomized controlled comparison of escitalopram and agomelatine, in which significantly more escitalopram-treated patients reported increased "lack of concern for issues previously of high importance" and a "lack of emotional intensity" (Corruble et al., 2011).

In an attempt to explore the effect of agomelatine on emotional processing as a proxy for emotional blunting, Harmer and colleagues (2011) evaluated the effect of agomelatine for 7 days in healthy volunteers, and demonstrated decreased recognition of sad facial expressions and improved positive affective memory in the agomelatine group. Although comparator drugs were not included in this study, previous trials using the same paradigms demonstrated impaired recognition of fear, anger and disgust with SSRIs (Harmer et al., 2004), supporting the hypothesis that agomelatine and SSRIs have disparate effects in term of emotional reactivity.

Cognitive Dimension

There is considerable evidence to suggest that deficits in memory function, executive function, attention, and psychomotor speed occur in patients with MDD (Austin, Mitchell, & Goodwin, 2001; Fossati et al., 1999; Porter et al., 2003). All medications with sedative effects have the potential to alter cognitive function. For example, tricyclic induced sedative and anticholinergic effects generally worsen pre-existing cognitive symptoms (Amado-Boccara, Gougoulis, Poirier, Galinowski, & Loo, 1992; Doraiswamy et al., 2003). Adverse effects of paroxetine on cognition have been linked to this drug's additional anticholinergic and sedative properties (Furlan et al., 2001). Among the SSRIs, sertraline has been associated with improvement in various neurocognitive components including attention, psychomotor speed and memory (Bandareff et al., 2000), and this may be associated with sertraline's additional dopaminergic effects. The favorable effects of SNRI antidepressants such as duloxetine on verbal memory (Raskin et al., 2007) and venlafaxine on a wider range of cognitive tasks (Cunningham et al., 1994) have been linked to positive norepinephrine effects on cognition. Similarly, effects on both norepinephrine and dopamine have been cited as possible mechanisms for bupropion's enhancement of attention, executive function, and psychomotor speed (Gualtieri & John, 2007). Overall, these findings suggest that improvement in cognition is not purely mediated by changes in depressive symptomatology, and that there are direct positive and negative effects of antidepressants on cognitive function.

To date, there are no published reports on the effects of agomelatine on specific aspects of cognitive function. However, subjective reports after one week of treatment reveal significant advantages on measures of "daytime alertness" and "feeling good" for patients receiving agomelatine compared to venlafaxine (Lemoine et al., 2007). In comparison with escitalopram, patients who received agomelatine reported a gradual progression of improvement in "clear thinking" during 24 weeks of treatment, which was not achieved in the escitalopram group (Quera-Salva et al., 2011). Similarly, "wellness on waking" improved more with agomelatine compared with escitalopram, also suggesting better alertness (Corruble et al., 2011). Future studies should evaluate the effect of agomelatine on all aspects of neurocognition.

Neurovegetative Dimension

The neurovegetative dimension includes symptoms such as sleep, energy, appetite, weight, libido and sexual function. The conventional cutoff score of 7 or less on the HRSD to describe remission (Frank et al., 1991) does not reflect the biases in symptom reduction that may occur during treatment. For example, an 8-week open-label study of fluoxetine therapy showed that responders who have not achieved remission had significantly more somatic symptoms than remitters (Denninger et al., 2006). Similarly, in an open-label treatment trial of SSRIs, venlafaxine, mirtazapine and bupropion, non-remitting responders had significantly smaller reductions in somatic items on both the HRSD and MADRS (McIntyre et al., 2006). Even among remitters, fatigue and sleep disturbance were the two most common residual symptoms following treatment with fluoxetine (Nierenberg et al., 1999). There is also evidence to suggest that antidepressants from distinct classes differentially affect somatic symptoms. Patients who did not respond to SSRIs had a significant reduction in somatic symptoms after treatment with mirtazapine (Fava et al., 2001).

Sleep and Alertness

Traditional antidepressants, including tricyclic and monoamine oxidase inhibitor agents, as well as Serotonin Reuptake Inbitiors and Serotonin Norepinephrine Reuptake Inhibitors frequently disrupt sleep. For example, desimpramine reduces sleep efficiency and increases wake time following sleep onset while SSRIs tend to disrupt continuity of sleep and may exacerbate bruxism and Restless Leg Syndrome (Wilson & Nutt, 2005).

The melatonergic action of agomelatine is particularly effective in the sleep-related disturbances of depressed patients. In a randomized controlled trial, primarily designed to evaluate the effect of agomelatine and sertraline on the rest-activity cycle, depressed patients receiving agomelatine reported significant benefits in "getting to sleep" and "quality of sleep" during the first week of treatment compared with sertraline (Kasper et al., 2010). In a comparison of agomelatine and escitalopram with polysomnography recordings, treatment with agomelatine was associated with a significant reduction in sleep latency from week 2 and an improvement in sleep efficiency (Quera-Salva et al., 2011). Somatic symptoms, as evaluated by the HAM-D scale, are also reduced by agomelatine in a metaanalysis of placebo-controlled trials (Demyttenaere, 2011). There is additional evidence from a large open-label trial that agomelatine improves energy and fatigue, where there was a 51% drop in the number of patients reporting daytime tiredness after 12 weeks of treatment (**Table 2**; Laux, 2011).

Libido and Sexual Function

Evaluation of sexual function incorporates desire, arousal and orgasm. While loss of sexual desire is present in approximately 70% of untreated depressed patients, treatment emergent adverse effects on all aspects of sexual function are associated

Table 2.
Effects of agomelatine on sleep (Laux, 2011).

Circadian Screen	Baseline (%)	12 weeks (%)
Difficulty falling asleep	74	12
Repeated awakenings	78	15
Daytime tiredness	62	11
Ability to carry out daily activities	33	61

with most SSRI and SNRI antidepressants (Kennedy & Rizvi, 2009). Since direct effects of serotonin on 5-HT$_{2C}$ receptors is thought to contribute to sexual side effects, it is not surprising that antidepressants with 5-HT$_{2C}$ antagonist properties are less likely to be associated with sexual dysfunction (Keltner et al., 2002). Mirtazapine has antagonistic effects on alpha-2 adrenergic, 5-HT2 and 5-HT3 receptors and agonist effects on postsynaptic 5-HT1A receptors. The 5-HT2 blockade is thought to be associated with low rates of sexual dysfunction (Waldinger, Zwinderman, Olivier, 2003).

Since agomelatine also has antagonist effects on 5HT2C, it was hypothesized that its effects on sexual function would be more favorable than venlafaxine in a randomized comparator trial. Results indicated a significant advantage of agomelatine in measures of desire in sexually active men and women who achieved remission, where approximately 20% in the venlafaxine group reported deterioration in desire, compared with 4% of those receiving agomelatine (Kennedy, Rizvi, Fulton, Rasmussen, 2008). In a subsequent study of healthy male volunteers, the effects of agomelatine at daily doses of 25 mg and 50 mg on sexual function were compared to paroxetine 20 mg in a placebo-controlled trial. The reported sexual side effects of agomelatine at both 25 mg and 50 mg were equivalent to placebo, whereas over 50% of patients on paroxetine reported treatment-emergent sexual side effects (Montejo et al., 2010).

Functional Outcomes

While the specific interactions among depression symptoms and function have not been empirically investigated, ultimately, all symptom dimensions have a potential impact on overall functioning. This concept is recognized in the DSM-IV definition of a major depressive episode, which requires a decline in function due to depressive symptoms, and is supported by high rates of patient reported dysfunction in occupational and social domains even after "remission" of a major depressive episode (Agosti & Stewart, 1998; Keller et al., 1987). Furthermore, the improvement of function is cited as a main goal of treatment based on clinical guidelines (Lam et al., 2009), and according to depressed patients, is perceived as a proxy for remission (Zimmerman et al., 2006). However, less than 5% of antidepressant clinical trials evaluate function as a treatment outcome (McKnight & Kashdan, 2009). The consequence of this is a failure to capture pertinent information that is different from basic symptom improvement. For example, in a 24-week study comparing duloxetine and escitalopram the remission rates did not differ at treatment end (73% vs 70%, respectively), although escitalopram treatment resulted in increased functioning based on the overall SDS score, as wel as the work subscale (Wade et al., 2007).

There is also evidence of improved function in several agomelatine trials in MDD (Stahl et al., 2010; Zajecka et al., 2010). In the MDD studies there was a significant improvement in overall functioning across work, social life, and family/home responsibility with agomelatine 25 mg (Stahl et al., 2010) and 50 mg (Zajecka et al., 2010) compared with placebo. Improvement in social functioning from the first week of treatment has also been demonstrated in an observational study with 111 depressed patients treated with 25 - 50 mg agomelatine (Novotny, 2011).

Further support for improved functioning with agomelatine is derived from a large naturalistic study of over 3300 outpatients who received agomelatine 25 - 50 mg for 12 weeks. Treatment effects on sleep and daily activity using a patient screening questionnaire were assessed in addition to conventional scale scores. At baseline, only 33% of patients were able to fulfill their normal daily activities, compared with 61% after 12 weeks of treatment (Laux, 2011).

Conclusion

Traditionally, primary measures of "treatment outcome" are restricted to changes in total scores on symptom scales such as HRSD or MADRS. The evaluation of symptom dimensions as well as function provides additional information that may discriminate between antidepressant agents and has the potential to refine treatment selection and improve outcomes. These approaches should be considered in the evaluation of new and emerging antidepressants such as agomelatine.

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