REVIEW

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Neuropsychiatric Adverse Effects of Centrally Acting Antiobesity Drugs

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SUMMARY

Introduction: Central neurochemical systems including the monoamine, opioid, and cannabinoid systems have been promising targets for antiobesity drugs that modify behavioral components of obesity. In addition to modulating eating behavior, centrally acting antiobesity drugs are also likely to alter emotional behavior and cognitive function due to the high expression of receptors for the neurochemical systems targeted by these drugs within the fronto-striatal and limbic circuitry. **Methods:** This paper reviewed the neuropsychiatric adverse effects of past and current antiobesity drugs, with a central mechanism of action, linking the adverse effects to their underlying neural substrates and neurochemistry. **Results:** Antiobesity drugs were found to have varying neuropsychiatric adverse event profiles. Insomnia was the most common adverse effect with drugs targeting monoamine systems (sibutramine, bupropion and tesofensine). These drugs had some positive effects on mood and anxiety and may have added therapeutic benefits in obese patients with comorbid depression and anxiety symptoms. Sedation and tiredness were the most common adverse effects reported with drugs targeting the m-opioid receptors (i.e., naltrexone) and combination therapies targeting the opioid and monoamine systems (i.e., Contrave™). Cognitive impairments were most frequently associated with the antiepileptic drugs, topiramate and zonisamide, consistent with their sedative properties. Drugs targeting the cannabinoid system (rimonabant and taranabant) were consistently associated with symptoms of anxiety and depression, including reports of suicidal ideation. Similar adverse events have also been noted for the D_1/D_5 antagonist ecopipam. **Conclusion:** These findings highlight the need to assess neuropsychiatric adverse events comprehensively using sensitive and validated methods early in the clinical development of candidate antiobesity drugs with a central mechanism of action.

Introduction

Obesity is a syndrome, which is increasingly viewed as having strong neurobehavioral components. Drug treatments for obesity have recently focussed on targeting central neurochemical systems including serotonergic, dopaminergic, endocannabinoid, and opioid systems. These neurochemical systems not only modulate brain areas associated with satiety, hedonic, and motivational eating behavior including the hypothalamus and the striatum, but also modulate areas within other limbic and fronto-striatal circuitry associated with the regulation of emotion. As a consequence of their non selective mechanisms of action, centrally acting antiobesity drugs are at risk of causing a number of neuropsychiatric adverse effects in a population with increased incidence of

psychiatric comorbidities including anxiety and depression. In this article, we review the neuropsychiatric adverse effects of antiobesity drugs with a central mechanism of action, based on findings in both animals and humans. These adverse effects will be discussed in relation to their underlying neural substrates and neurochemistry to highlight neurochemical targets that are most likely to be associated with increased psychiatric risk.

Neuropsychiatric Correlates of Obesity

Obesity is associated with high prevalence of neuropsychiatric comorbidities including anxiety and depression. Early epidemiological studies have provided some evidence linking increased weight with incidence of psychiatric symptoms [1,2]. Clinical observations since the turn of the century have also suggested that obesity may be associated with increased incidence of depression [3]. However, a number of community based studies failed to find any association between obesity and depression [4–6], although these early inconsistencies have been attributed to methodological factors including failure to use DSM-IV criteria for assessment of depression. In support of an association between obesity and psychiatric comorbidities, a large population based study conducted in the United States in approximately 40,000 subjects using DSM-IV criteria, found an increased incidence of depression were found, with a 37% increase in the probability of being diagnosed with major depression in obese females [7]. In this study relatively increased body weight and body mass index (BMI) were associated with higher incidence of major depression, suicide ideation and attempts [7]. In another large study investigating 14-day sustained depressive mood in the previous month in 44,800 adults, young females (age 18–24) with a BMI $\geq$25 kg/m^2 had an increased prevalence of sustained depressive moods compared to nonoverweight/nonobese women [8]. A more recent study in 253 obese patients from two specialist weight management clinics in the United Kingdom found elevated scores of depression in 48% and elevated scores for anxiety in 56% of patients, with a higher (60%) incidence of anxiety in females [9]. This study also showed that the probability of reaching scores suggestive of "probable" or "severe" anxiety or depression, increased in both males and females with increases in BMI. The neuropsychiatric findings are consistent with observations that obesity is also associated with increased incidence psychological characteristics such as low self-concept and negative attributions of life events [10]. Together these findings highlight the high prevalence of anxiety and depression amongst obese patients and the need to carefully evaluate the potential adverse neuropsychiatric risks when considering treatment options. Certain pharmacological treatments could potentially exacerbate these symptoms whilst others may have no effect or even attenuate them. The next section of the article will discuss a number of key neurotransmitter systems targeted by centrally acting antiobesity drugs to assess the documented and likely risks of neuropsychiatric adverse effects.

The Monoamine System: Indirect Agonists and Subtype Selective Receptor Antagonists

Serotonin and Noadrenaline Reuptake Inhibitors

A number of drugs targeting the serotonin system have been investigated for their antiobesity efficacy, although their exact mechanism of action is yet to be determined. Drugs such as fenfluramine and dexfenfluramine (serotonin reuptake inhibitor and releaser) were used as antiobesity agents [11], but were subsequently withdrawn from the market due to the development of cardiac valvular diseases. A number of selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline and citalopram) were shown to induce short-term weight loss but failed to achieve sustained weight loss in the treatment of obesity [12]. Sibutramine, a serotonin and noradrenaline reuptake inhibitor was found to have longer-term efficacy (24 weeks) in the treatment of obesity [13] and was subsequently approved by the Food and Drug Administration (FDA) for the treatment of obesity. The anorectic effects of sibutramine (and its metabolites) are thought to be mediated via α_1 and β_1-adrenergic and 5-HT$_{2B/2C}$ receptor mechanisms [14,15], while its thermogenic effects are thought to be mediated by stimulating β_3 adrenoceptors in brown adipose tissue [16,17]. Modulating serotonin and noradrenaline neurotransmission would also be expected to have effects on emotion including anxiety and depression via the modulation of multiple serotonin and noradrenaline receptors within the fronto-limbic circuitry. Indeed, serotonin and noradrenaline reuptake inhibitors are effective anxiolytic and antidepressant drugs.

At the time of approval, it was generally accepted that dexfenfluramine did not increase the risk of neuropsychiatric adverse effects [18,19]; however, a review of some individual case reports indicate adverse events including mood swings, depression and anxiety [20]. Studies conducted with sibutramine indicate that it has a low risk profile for neuropsychiatric adverse effects. In fact, a number of studies have shown evidence for an antidepressant effect of sibutramine, consistent with

its mechanism of action. For example, an open labeled study of sibutramine (15 mg) in obese patients showed a reduction in depression scores (assessed using the comprehensive psychopathological rating scale, [21]) over 6 months of treatment [22]. In a more controlled trial with a comparison group (low calorie diet), 3 months' treatment with sibutramine (10 mg) (plus a low calorie diet) was associated with a decrease in depression scores as assessed by the Hamilton Depression Rating Scale (HAM-D) in obese and overweight subjects [23]. These findings in obese patients support those of a placebo controlled study conducted in patients with Binge Eating Disorder (BED), where sibutramine (15 mg) over 3 months of treatment, reduced depression scores as assessed by the Beck Depression Inventory (BDI) [24].

There are however sporadic case reports of sibutramine induced neuropsychiatric adverse effects reported in the literature including panic attacks [25], psychotic episode [26,27], delusional disorder [28], hypomanic/manic episode [29,30], and amnesia [31]. Although the neural basis of these adverse effects is unclear from these single case reports, they have been linked to sibutramine treatment and may represent a real risk under certain environmental conditions (i.e., stress) and/or in patients that have a genetic predisposition (i.e., family history of psychiatric disorders). These rare adverse events were also noted (one or two individual cases of each) in a large observational cohort study (in approximately 12,300 patients) using prescription event monitoring in England [32]. This study also showed that depression (an incidence of 0.8%) and insomnia (an incidence of 0.7%) were two neuropsychiatric adverse events that led to patients stopping sibutramine within 3 months of treatment initiation. Overall, the risks of neuropsychiatric adverse effects following sibutramine treatment appear to be low, although the risks may be higher in patients who have a current diagnosis or a family history of psychiatric disorders. In fact, sibutramine is contraindicated in patients with severe depression or preexisting mania due to the concern that it may have the potential to cause greater adverse effects [33].

5-HT_{2C} Agonists

The efficacy of fenfluramine and other indirect serotonin agonists, including SSRIs, provided evidence that stimulating central serotonin receptors may be an effective pharmacological mechanism to suppress appetite and reduce body weight. More recently, serotonin agonists that specifically activate serotonin 2C (5-HT_{2C}) receptors have been shown to increase satiety and reduce food intake [34–36]. 5-HT_{2C} receptors are found in many areas important for regulating food intake including the limbic structures and the hypothalamus [37] and activation results in stimulation of anorexigenic pro-opiomelanocortin (POMC) neurons in the hypothalamus [38,39]. Lorcaserin is a selective 5-HT_{2C} agonist that has recently been shown to produce weight loss over a 12-week period in patients with obesity [36]. In this study, no neuropsychiatric adverse events were reported (based on the Visual Analogue Mood Scales [VAMS]) consistent with prediction that neuropsychiatric adverse events are primarily caused by 5-HT_{2A} receptor activation. However, the VAMS is not a sensitive measure of clinically relevant neuropsychiatric adverse events and while lorcaserin appears to have minimal neuropsychiatric adverse events based on this study, potential adverse events should be assessed using more sensitive measures of clinical symptoms (see Section "The Endocannabinoid System: CB1 Receptor Antagonists" for further discussion) and risks should be reevaluated when such data are available.

Dopamine and Noradrenaline Reuptake Inhibitors

The dopamine system has been targeted for the treatment of obesity supported by the evidence that enhanced dopamine neurotransmission stimulates POMC neurons in the arcuate nucleus of the hypothalamus [40,41]. A number of studies have shown weight reduction with bupropion, a dopamine (and noradrenaline) reuptake inhibitor [42]. Enhancing dopamine and noradrenaline neurotransmission is also expected to modulate emotion including reward, mood, and anxiety via specific effects within the ventral striatum, amygdala, and the prefrontal cortex. Psychiatric adverse effects following bupropion treatment have been low, although there are reports of insomnia and anxiety. In the first study of bupropion (200 mg for 8 weeks) in overweight and obese women, there was higher (although nonsignificant) incidence of insomnia (20% compared to 4% with placebo) and nervousness (4% compared to 1% with placebo) [41]. Similarly, in another study in obese patients (300 and 400 mg sustained release [SR] bupropion for 24 weeks), early withdrawals due to adverse events were mainly due to insomnia or anxiety [43]. However, bupropion treatment was associated with a significant decrease in the depression scores as assessed using the BDI. An antidepressant effect was supported in a study in obese patients with depressive symptoms, where bupropion (300 mg SR over 26 weeks) was shown to reduce depressive symptoms in a subgroup of patients with a history of major depression [44]. In this study, the incidence of insomnia was not different to that reported under placebo treatment.

The studies conducted on bupropion suggest a low incidence of neuropsychiatric adverse effects with some

reports of insomnia and anxiety. There are case reports describing psychosis, however, this adverse effect is uncommon and is most likely due to other factors (i.e., concomitant cannabis use) [45,46].

Noradrenaline, Dopamine and Serotonin Reuptake Inhibitors

Tesofensine, a triple reuptake inhibitor that inhibits the presynaptic uptake of noradrenaline, dopamine, and serotonin, was recently shown to reduce weight in obese patients with Parkinson's and Alzheimer's disease without affecting mood [47]. In a subsequent Phase II study investigating the safety and efficacy of tesofensine (0.25–1 mg for 24 weeks) in patients with obesity, weight loss of up to 10.6% (twice that of Sibutramine) was reported [48]. Using the POMS to measure mood states, no significant changes in total mood disturbance, depression or dejection, anxiety or tension, fatigue or inertia were reported (in comparison to placebo). However, there was an increased incidence of depressed mood in the tesofensine group (approximately 6% in the 0.5 and 1 mg groups) including 1 case (2%) of major depression at the highest dose (1 mg). This dose was also associated with increased anger and hostility and both the 0.5 and 1 mg doses caused greater confusion. Other adverse effects included a tendency for increased agitation and insomnia [48]. Given that mood was only assessed using the POMS, a more comprehensive assessment of neuropsychiatric adverse events is warranted in future studies. Overall, the studies conducted to date on tesofensine suggest low incidence of neuropsychiatric adverse events.

Dopamine and Noradrenaline Reuptake Inhibitors and Releasers

A number of amphetamine derivatives including phentermine are currently used in the United States for the short-term treatment of obesity (less than 12 weeks). These drugs have greater sympathomimetic effects (i.e., cause larger increases in catecholamine release) due to their dual pharmacological action as a dopamine and noradrenaline reuptake inhibitor and releaser. As a consequence phentermine, like amphetamines, has the potential for addiction and abuse and is classified by the US Drug Enforcement Agency (DEA) as a schedule IV drug [49]. No other significant neuropsychiatric adverse effects have been reported with phentermine, except for insomnia (up to 35% of cases) [50,51]. This adverse event is consistent with evidence of increased arousal and vigor measured using the POMS following phentermine administration in healthy subjects [52]. However, there are case reports of more serious neuropsychiatric adverse effects following phentermine treatment, including psychotic episodes [53–56], mania [57] and sporadic incidence of depression and irritability in clinical studies [58].

D_1/D_5 Antagonists

Dopamine receptors, and in particular the D_1/D_5 dopamine receptor have been explored as a potential target for treating obesity. This is primarily based on the evidence that D_1 receptor knockout mice show reduced sucrose reinforcement [59] and a prototype D_1/D_5 antagonist decreased consumption of preferred flavors in rats [60]. Recently a study reported findings from human phase 2 and phase 3 clinical trials examining the potential of the D_1/D_5 receptor antagonist, ecopipam, to enhance and maintain weight loss in obese patients [61]. While these studies showed promising weight loss in both phase 2 and phase 3, there were unexpected treatment related neuropsychiatric adverse events (ecopipam 31% vs. placebo 15%) in the phase 3 clinical trials (that were not observed in the phase 2 studies) and as a consequence phase 3 studies were discontinued. The neuropsychiatric adverse events included depression (ecopipam 16% vs. placebo 6%), anxiety (ecopipam 15% vs. placebo 6%), suicidal ideation (ecopipam 2% vs. placebo 1%), insomnia (ecopipam 17% vs. placebo 7%), fatigue (ecopipam 15% vs. placebo 6%), and somnolence (ecopipam 15% vs. placebo 4%). Psychiatric adverse events also accounted for more than half of the discontinuations because of treatment related adverse effects in the ecopipam group.

While the mechanisms contributing to the neuropsychiatric adverse events are not known, it is possible that reducing dopaminergic neurotransmission (including compensatory changes in D_1 receptors) by D_1/D_5 receptor antagonism could in part provide a mechanistic explanation for the adverse events. It is unclear why similar adverse events were not detected in the earlier phase 2 study and while it is possible that this may be related to duration of treatment (12 weeks phase 2 study vs. 52 weeks phase 3 studies), it is also possible that insensitive questionnaires were used to detect neuropsychiatric adverse events in the phase 2 studies (the type of questionnaires and clinical assessments used in both phase 2 and 3 studies were not reported).

The Opioid System: μ-opioid Receptor Antagonists

Since the first evidence that opioid peptides have a role in modulating eating behavior [62], the opioid system and, in particular, μ-opioid receptors (MORs), has been

explored as a potential target for modulating hedonic and motivational eating behavior [63]. Currently there are no approved drugs for the treatment of obesity which specifically target opioid receptors, although, the nonselective opioid antagonist naltrexone was examined as a potential antiobesity drug and currently a number of pharmaceutical companies are actively pursuing research with more selective μ-opioid receptor antagonists and inverse agonists for the treatment of obesity either as monotherapy or as an adjunctive therapy with other centrally or peripherally acting antiobesity drugs. MORs are largely distributed within the limbic areas of the brain including the nucleus accumbens, ventral tegmental area (VTA), and amygdala [64]. While these areas are important in modulating reward and food intake, they are also fundamental in regulating other emotional responses. As a result, drugs targeting MORs would be expected to have a range of behavioral effects including changes in mood and emotional wellbeing, although such effects are poorly characterized.

Preclinical studies have shown that nonselective opioid receptor antagonists such as naloxone and naltrexone tend to exert anxiogenic effects in animal models [65,66] and mice deficient in preproenkephalin are more anxious and display aggressiveness [67]. The effects of opioid antagonists on anxiety and depression related behavior is likely mediated by selective modulation of opioid receptors as mice lacking the delta- (δ) opioid receptors (but not kappa- [κ] opioid receptors) show anxiety and depressive like behaviors in animal models of anxiety (i.e., elevated plus maze and the light-dark box) and depression (i.e., forced swim test and conditioned suppression of motility paradigm) [68]. Interestingly, mice lacking MORs showed a decrease in the induction of anxiety and depressive like behaviors in these models [68]. These findings suggest a possible homeostatic interaction between δ- and μ-opioid receptors in the regulation of mood states with activity via the δ-opioid receptors (and reduced activity via μ-opioid receptors) facilitating anxiolytic or antidepressive like effects. In theory, the preclinical evidence would suggest that the greater the selectivity of the antagonist for μ-opioid receptors (relative to δ), the less likely it would be to cause adverse effects on mood and anxiety.

Consistent with animal studies, nonselective opioid receptor antagonists have been shown to cause studies some mild dysphoria in healthy subjects. One of the first demonstrations linking naltrexone with depression was a study in a small number of healthy drug naïve subjects with no history of opioid or other drug use, where a range of unpleasant symptoms including dysphoria, fatigue, and sleepiness were reported following naltrexone (50 mg) treatment [69]. Subsequent studies have reported mild depression or dysphoria with naltrexone treatment in healthy subjects (assessed using the Profile of Mood States; POMS [70]) [71] or in a very small group of opioid free-former addicts [72]. However, depression has not been a frequent treatment-emergent adverse event in clinical studies in alcoholics or opiate addicts treated with naltrexone. For example, long-term naltrexone treatment studies in alcoholics [73,74] or opioid addicts undergoing behavioral therapies [75–77] have not reported occurrence of dysphoria or depression. This may in part be related to long-term changes to the opioid system (including changes in opioid receptor expression and opioidergic tone) following chronic drug use. For example, in a study of naltrexone in alcohol dependent subjects, overall depressive symptoms were found to be improved in naltrexone and placebo treated patients over time, although a higher proportion of patients in the naltrexone treated group displayed elevated depression scores [78]. In opioid addicts, naltrexone has been associated with improvement in depressive symptoms as assessed using the POMS and Symptom Checklist-90 Revised (SCL090-R) [79,80]. Miotto et al. [79] did however report an increased incidence of suicide due to opioid overdose, but this was not thought to be linked to naltrexone administration. In another study in opioid dependent subjects, naltrexone (50 mg) treatment for 6 months was not associated with worsening of depressive or anxiety symptoms as assessed using the BDI and State-Trait Anxiety Inventory (STAI) [81]. Consistent with previous studies, there was a trend for an improvement in depression with naltrexone treatment.

The effects of naltrexone on mood symptoms have also been examined in obese and overweight subjects. In one study, high dose naltrexone (300 mg) treatment over 8 weeks had no effects on mood (assessed using the POMS and the BDI) or cognitive function in overweight subjects [82]. Another study in obese subjects showed no effects of 8-week naltrexone treatment on mood as assessed using the POMS [83]. However, one participant discontinued the study because of a severe dysphoric reaction. The authors have suggested that perhaps subpopulations of patients under physiological or psychological stress may react to naltrexone with dysphoric symptoms. This has not been directly investigated, but there is evidence that the opioid system within areas of the limbic circuit could modulate the stress response in animals (i.e., opioids have been shown to reduce stress related neuroendocrine and autonomic responses) [84] and activate the hypothalamic–pituitary–adrenal (HPA) axis in humans [85,86].

Overall, studies conducted in clinical groups suggest minimal effects of naltrexone or opioid receptor antagonism on depression or anxiety symptoms [74].

However, the evidence for dysphoric episodes in studies performed in healthy subjects, together with individual reports of similar adverse events in clinical studies, suggests a potential risk that needs to be monitored clinically. It is possible that in vulnerable individuals under conditions of stress, there may be a higher incidence of neuropsychiatric adverse effects such as anxiety and depression. While the majority of studies have primarily reported depression, dysphoria or anxiety, a number of other adverse effects have been consistently reported following naltrexone treatment. In an open-label study of 570 alcoholics seeking treatment, common neuropsychiatric complaints included nervousness (4%) and fatigue (4%) [87]. In another study examining data from two naltrexone trials for alcohol relapse prevention [88,89], the most prevalent neuropsychiatric adverse effects (of moderate to severe tested using a symptoms check list) were tiredness (31.5%), sleepiness (29.3%) and drowsiness (21.4%) [90].

The mechanisms responsible for opioid induced regulation of sleep/sedation are poorly understood. Further, the opioids have complex effects on sleep architecture. For example, clinically relevant doses of opioid agonists such as morphine increase wakefulness and decrease sleep behavior as measured by electroencephalography (EEG) of nonrapid eye movements (NREM) sleep, rapid eye movement (REM) sleep and sleep efficiency [91,92]. While it is unclear which subtype of opioid receptors may be responsible for the sedative like effect (tiredness and sleepiness), there is evidence for a μ-opioid receptor mediated effect in sleep centers in the brain including the medial pontine reticular formation (PRF) and ventrolateral preoptic nucleus (VLPN) [93,94]. VLPN infusion of the μ-opioid agonist DAMGO has been shown to decrease total sleep time and REM sleep, while the μ-opioid receptor antagonist CTAP increased total sleep [94]. The latter finding is also consistent with the evidence that intravenous naloxone (a μ-opioid receptor antagonist) increased delta wave sleep in rats [95]. Similarly, PRF injection of the μ-opioid receptor agonists morphine and DAMGO (but not δ or κ agonists) increased wakefulness and decreased REM and NREM sleep in rats [93,96]. Hence it possible that, at least within the VLPO and PRF, endogenous opioids acting via μ-opioid receptors maintain arousal and μ-opioid antagonists may induce sedation/sleepiness by reducing arousal.

Recently it was demonstrated that the naltrexone dose (50 mg) used in previous clinical studies occupies greater the 95% of MORs [97], suggesting that this dose may have been too high and the saturation of MORs may have contributed to the reported sedative like adverse events. Furthermore, this dose of naltrexone was also been shown to occupy δ-opioid receptors and it is possible that some of the mood effects may be secondary to antagonism or inverse agonism of δ-opioid receptors. Hence, it is possible the neuropsychiatric adverse events could generally be reduced by selecting doses that achieve lower receptor occupancies (particularly at δ-opioid receptors), although the challenge would be to simultaneously maintain adequate receptor occupancies at the μ-opioid receptors to achieve therapeutic efficacy.

The Endocannabinoid System: CB_1 Receptor Antagonists

The endocannabinoid system has been an important pharmacological target for novel antiobesity drugs [98,99]. The cannabinoid type 1 (CB1) receptors are widely distributed in the central nervous system, located mainly in presynaptic terminals of neurons [100] and in particular, on GABAergic interneurons expressing the α_2 subunit enriched $GABA_A$ receptors [101,102]. The expression of CB1 receptors is particularly high within areas of the brain associated with regulation of emotion, including the prefrontal cortex, hippocampus, amygdala, and periaqueductal gray [100,103], suggesting that drugs modulating the CB1 receptor may induce anxiety or depressive like behaviors. While the exact mechanism linking CB1 receptor modulation and emotional regulation is not known, inhibition of GABA release from axon terminals of local-circuit GABAergic interneurons in areas like the amygdala by presynaptic CB1 receptors may constitute an important mechanism underpinning the neurobiological substrates of CB1 mediated emotional responses [102]. Consistent with the proposed neurochemical mechanism, CB1 knockout mice have been shown to have increased anxiety in several animal models of anxiety [104–107] and also show profound deficits in the learned inhibition of fear (i.e., fear extinction) [108]. Furthermore, impaired CB1 signaling has been shown to exacerbate stress coping behavior [109], while CB1 receptor antagonists including SR141716A (rimonabant) and AM-251 have been shown to increase anxiety related behavior in animal models of anxiety [104,110–112] and impair fear extinction [113]. These studies are also supported by the findings that CB1 receptor modulation and environmental stress interact at the level of the amygdala [114], CB1 knockout mice have higher basal activity of the HPA-axis [109,115], and CB_1 antagonists rimonabant and AM-251 increase basal and stress induced corticosterone levels [109,115].

Despite preclinical evidence suggestive of adverse neuropsychiatric effects in animal models, rimonabant, the first of the CB1 receptor antagonists to be marketed in Europe, was developed as an antiobesity agent. While

there are no published studies on neuropsychiatric adverse events from early phase 1/II studies of rimonabant, there were some reports that rimonabant had good tolerability in 7 day and 16 week Phase 1/II studies in overweight and obese subjects [116–118]. However, in June 2007, the US Food and Drug Administration (FDA) expressed concern regarding neuropsychiatric adverse effects of rimonabant in Phase III studies (i.e., Acomplia Clinical Development Program) and in November, 2008, the drug was withdrawn from the European market. These concerns were triggered from a number of studies (rimonabant in Obesity [RIO]) conducted in obese patients with no history of psychiatric disorders including depression, which reported increased incidence of psychiatric disorders (up to 9.5%), including anxiety (up to 3%) and depression (up to 3.6%) measured using the Hospital Anxiety and Depression (HAD) scale [119–123]. In a meta-analysis of these RIO studies, patients receiving rimonabant (20 mg) were 2.5 and 3 times more likely to discontinue treatment because of depressive or anxiety symptoms respectively [124]. The FDA further examined the same studies as the latter meta-analysis did not provide detailed information regarding the rates of neuropsychiatric adverse effects. This report found that 26% of rimonabant treated (vs. 14% of placebo treated) patients had an adverse neuropsychiatric event [125]. Further, 9% of rimonabant treated (vs. 5% placebo treated) patients reported symptoms of depression (i.e., depressed mood, depression, depressive symptoms, or major depression). Other frequently reported symptoms with rimonabant treatment were either anxiety or sleep related. These adverse events included higher incidence of irritability (1.93% for rimonabant vs. 0.56% for placebo), insomnia (5.42% for rimonabant vs. 3.31% for placebo), nervousness (1.42% for rimonabant vs. 0.31% for placebo) and panic attacks (0.83% for rimonabant vs. 0.06% for placebo).

The FDA also reported findings related to suicide based on analysis of 13 studies where suicidality was adjudicated by the Columbia University group. In this analysis, rimonabant was associated with a 1.9 higher risk for suicidality (primarily based on measures of suicidal ideation) compared to placebo [125]. However, it should be highlighted that suicidal ideation does not imply likely translation to completed suicides and is likely to represent only an increased suicidal risk [126,127]. More recent studies conducted in diabetic patients (SERENADE study) [128], smokers (CIRRUS study) [129] and obese patients with metabolic syndrome [130] have similarly reported increased incidence of neuropsychiatric adverse effects and in particular depression or anxiety related symptoms following rimonabant treatment. In a study investigating the risk of discontinuation due to adverse events from data gathered from five rimonabant studies, it was reported that 47% of dropouts were due to psychiatric causes including suicidal ideation [131]. Finally, it is worth highlighting a study performed in patients with atherosclerosis (STRADIVARIUS study) [132], where patients with psychiatric disorders were not excluded and rimonabant (20 mg) treatment was associated with even higher levels (43.4% in rimonabant treated compared to 28.4% in placebo treated) of neuropsychiatric adverse effects (particularly anxiety and depression). This finding provides important evidence of an increased risk of neuropsychiatric adverse effects in patients who already have existing psychiatric disorders.

Taranabant is another drug targeting CB1 receptors (CB1 inverse agonist) developed for obesity by Merck Research Laboratories. Following the adverse neuropsychiatric findings with rimonabant and CB1 receptor antagonism, Merck announced the suspension of all research with this drug in October, 2008. In a study, reporting weight loss in obese patients with no current or history of psychiatric disorders, taranabant was associated with a 30% increase in neuropsychiatric adverse effects (including anxiety, nervousness and depressed mood or depressive symptoms) compared to placebo (19%) [133] assessed using the Patient Health Questionnaire 9 (PHQ-9) [134] and the POMS. In this study, 15% of patients who experienced neuropsychiatric adverse effects discontinued the study due to those adverse effects. A single dose [135] and repeat dose study [136] of taranabant in healthy subjects also showed evidence for a dose related increase in neuropsychiatric adverse experiences (i.e., mood changes). Interestingly, in both these studies, no changes in mood were observed when assessed objectively with the VAMS highlighting the lack of sensitivity of this particular mood scale in detecting clinically relevant neuropsychiatric adverse events at an early stage in drug development. The use of clinically sensitive measures of mood including the BDI, Beck Anxiety Inventory (BAI) and HAD scale instead of measures like the VAMS, may provide an earlier indication of clinically relevant neuropsychiatric adverse events and failure to use these measures in the later studies [135,136] may have led to underestimation of potential neuropsychiatric adverse events.

The reviewed literature from preclinical and clinical studies provides strong evidence in support of CB1 receptor antagonism causing an increased incidence of neuropsychiatric adverse effects, and in particular, depression, and anxiety. While CB1 receptor modulation showed tremendous promise as a novel target for antiobesity efficacy, it's now apparent that this mechanism cannot be pursued further due to the serious neuropsychiatric risk.

Broad Spectrum Neurotherapeutic Agents: Topiramate and Zonisamide

The antiepileptic medication topiramate has been shown to cause weight loss in both rodent models of obesity and obese patients [137,138]. While the mechanisms associated with this weight loss are not fully understood, a number of pharmacological effects including a reduction in glutamate transmission (via AMPA/kainate glutamate receptors) [137,139], stimulation of lipoprotein lipase activity in brown adipose tissue and skeletal muscle [137,140], and indirect modulation of dopaminergic neurotransmission [141], may provide a mechanistic basis. While topiramate shows significant weight loss in obese patients, it has been shown to consistently cause a number of neuropsychiatric adverse events. In a 6-month dose ranging study in obese patients (64–384 mg/day), the most common adverse events reported included difficulty in memory (11–28% topiramate vs. 8% placebo), difficulty in concentration/attention (7–12% topiramate vs. 5% placebo), nervousness (4–11% topiramate vs. 3% placebo), anxiety (3–8% topiramate vs. 0% placebo), and depression (3–10% topiramate vs. 3% placebo) [142]. These adverse events were dose related and were more frequently reported in the initial dose titration period. In a larger dose ranging study (96–256 mg/day) in obese patients, a similar profile of neuropsychiatric adverse events was reported including difficulty in memory (9–13% topiramate vs. 7% placebo), difficulty in concentration/attention (10–12% topiramate vs. 3% placebo), nervousness (4–6% topiramate vs. 2% placebo), mood problems (5–9% topiramate vs. 4% placebo), and depression (7–13% topiramate vs. 8% placebo) [143]. Again, these adverse events were mostly observed in the early dose titration phase of the study. Of most concern were adverse events related to suicidality. Two subjects reported suicide attempt and four subjects reported suicidal ideation (five of the cases thought to be drug related). The study was terminated early by the sponsor in light of these adverse events.

A number of more recent studies conducted in obese patients [144], obese type 2 diabetic patients [145–147] and binge eating disorder associated with obesity [148] have similarly reported higher incidence of cognitive impairment, depression/mood problems and anxiety/nervousness following topiramate treatment. It is unclear from these studies how cognition and changes in mood were assessed and hence the clinical significance of these impairments remains unknown. However, studies in obese patients with binge eating disorder have shown no clinically significant changes in depression or anxiety, using clinically validated questionnaires including the Montogomery-Asberg Depression Rating Scale (MADRS), Hamilton Depression Scale (HAM-D) and Hamilton Anxiety Scale (HAM-A) [148,149].

Zonisamide is another antiepileptic drug, which was initially reported to cause weight loss as an adverse event in patients with epilepsy [150]. Studies performed in patients with obesity [151] and binge eating disorder with obesity [152], have shown significant weight loss over 3 months. The mechanisms associated with the antiobesity effects are poorly understood but may be linked to its modulation of the dopaminergic and serotonergic systems [153,154]. In a 16-week study in obese patients, zonisamide (dose escalated from 100 to 600 mg/day) was well tolerated with only a few adverse events (i.e., sedation in 33% of patients) [155]. However, in this study adverse events were not gathered using objective questionnaires or neuropsychological tests, but instead, using spontaneous reporting by patients and open-ended inquires by clinicians. In an open label study in patients with binge eating disorder, the profile of neuropsychiatric adverse events was similar to topiramate and included sedation (47%), drowsiness (33%), memory and cognitive impairment (27–40%), panic symptoms (13%), and depression (13%) [152]. In a small randomized controlled study in obese patients with binge eating disorder, more adverse events were noted following zonisamide compared to placebo (although there were no significant group differences) [156]. Consistent with previous studies, the more common neuropsychiatric adverse events included somnolence (40% zonisamide vs. 23% placebo), nervousness (27% zonisamide vs. 10% placebo), thinking abnormality and amnesia (17% zonisamide vs. 10% placebo), dizziness (13% zonisamide vs. 7% placebo), and insomnia (13% zonisamide vs. 7% placebo). There were no changes in clinical depression as assessed by the HAM-D scale [156].

Studies with the antiepileptic drugs topiramate and zonasimide show consistent impairments in cognitive function (i.e., attention and memory), which may be associated with their sedative properties. The published studies do not provide detailed information about the tests used to probe the cognitive deficits, although from the reported data, it is likely that objective and sensitive methods of cognitive testing were not utilized and hence it is likely that these studies could be under reporting the true deficits. Mood changes (depression and anxiety) have also been reported in obese patients administered these drugs, and again, it is unclear if clinically accepted and validated questionnaires were used in many of the studies in obese patients. The studies performed in patients with binge eating disorder using such methods have reported no changes in clinical depression. Similar rigorous assessment of mood, anxiety and suicidality is required for future studies with these compounds in

obese patients for the reasons outlined in Section "Neuropsychiatric Correlates of Obesity."

Combination Treatment Strategies Targeting Multiple Neurochemical Systems

Recently, it has been suggested that combining the μ-opioid antagonist naltrexone with the dopamine and noadrenaline reuptake inhibitor, bupropion could lead to greater therapeutic profile based on the hypothesis that naltrexone (or μ-opioid receptor antagonism) would block the normal inhibitory feedback mechanism that limits sustained POMC activation in response to a dopaminergic drug such as bupropion [155]. Contrave™, under development by Orexigen Therapeutics Inc, is an oral SR combination treatment comprising bupropion (360 mg/day sustained release) and naltrexone (32 mg/day sustained release) for the potential treatment of obesity. Currently, there are a number of ongoing trials and findings from completed phase II and III studies that provide evidence for enhanced efficacy of the combination strategy [157–159]. While a combination strategy such as this may have enhanced therapeutic efficacy, the incidence of adverse effects may also increase, especially if both drugs have a central mechanism of action. In early phase II studies the most common neuropsychiatric adverse effect reported was insomnia with no changes reported on anxiety and depression scores as assessed by the 17-item Hamilton Depression Scale (HAMD-17) Maier subscale, the HADS questionnaire, and a mood (suicidality) questionnaire [159]. In a Phase III trial in obese and overweight patients (over 56 weeks), neuropsychiatric adverse effects were examined with the most frequent adverse effects reported with Contrave™ and placebo respectively, including insomnia (8.7 and 6.0%), anxiety (5.1 and 3.5%) and depressed mood (1.9 and 4%) [157–159]. The overall rate of neuropsychiatric adverse effects was similar for both treatments (25% vs. 22.5% for Contrave™ and placebo, respectively) and no differences were observed for withdrawal rates due to neuropsychiatric adverse effects [158]. It is worth noting that the effects of Contrave™ were examined in patients receiving adjunctive behavioral therapy and it is unknown if the low neuropsychiatric adverse event profile would be seen in patients without such therapy or in patients with a history of depression or anxiety disorders.

Other combination treatments currently in development include Qnexa (VIVUS Inc), a combination of low dose topiramate and phentermine and Empatic (Excalia; Orexigen), combination of bupriopion and zonisamide. There are no published studies on these compounds, but based on the neuropsychiatric adverse event profile reviewed, higher incidence of insomnia and cognitive impairment may be predicted.

Conclusion

Centrally acting antiobesity drugs modulate a number of neurochemical systems involved in the regulation of mood, reward, cognition and sleep. As such, these drugs could be expected to cause a number of neuropsychiatric adverse effects. The most commonly reported adverse effects of centrally acting antiobesity drugs reviewed were anxiety related (nervousness, anxiety), depression related (mood changes, depression, suicidal ideation), sleep related (insomnia, fatigue, tiredness), or cognition related (i.e., attention or memory impairments). There were also rare adverse events reported including psychosis and mania. Drugs targeting the monoamine systems (i.e., sibutramine, buproprion, and tesofensine) that enhance monoamine neurotransmission, have a relatively low incidence of neuropsychiatric adverse events with the most common adverse event reported being insomnia. This class of drugs appears to have some positive effects on mood and anxiety and hence may have added therapeutic benefits in obese patients with comorbid depression and anxiety symptoms. Sedation and tiredness were common adverse events reported with μ-opioid receptor antagonists. The antiepileptic drugs topiramate and zonisamide were associated with significant cognitive impairments, which may also be linked to their sedative properties. The combination therapy, Contrave™ was associated with higher incidence of insomnia and anxiety and the risk profile needs to be further assessed following completion of Phase III studies. The CB_1 receptor antagonists including rimonabant were associated with the highest incidence of neuropsychiatric adverse events including anxiety, depression and suicidal ideation. Similar adverse events have also been reported for the D_1/D_5 antagonist, ecopipam. The higher incidence of mood adverse events with CB_1 and D_1/D_5 receptor antagonists may in part be related to the common mechanism of reducing dopamine neurotransmission in the limbic circuitry. Overall, the findings highlight the need to assess neuropsychiatric adverse events comprehensively using sensitive and validated methods throughout the development of candidate antiobesity drugs. With all centrally acting drugs, there is the potential for higher incidence of neuropsychiatric adverse events in vulnerable individuals (e.g., those with a family history of psychiatric disorders, children, and adolescents and/or those living under high stress) and this risk should be evaluated in future studies.

Opinion

Unlike many chronic diseases such as diabetes, the bar for the safety of centrally acting obesity drugs is set much higher by regulatory agencies, thus making drug discovery in this area highly challenging with an inherent risk of failure due to development of neuropsychiatric adverse events. The rimonabant example highlights the risks associated with developing centrally active agents, particularly agents that also modulate neurochemical systems involved in the regulation of sleep, anxiety or depression. There are important lessons that could be learnt from the rimonabant story, which may help future drug discovery efforts, particularly in relation to identifying neuropsychiatric adverse events early in drug development. It is unclear why drug development continued up until 2008 when data were emerging as early as 1997 in published papers of potential anxiogenic effects of CB_1 antagonists in animal models of anxiety. It is possible that the uncertainty of how the preclinical data translate to humans, inconsistencies in the data gathered in preclinical models, or a continued effort to optimize a weight loss dose with a nondepressant/anxiogenic effect may have contributed to the decision to continue the development into phase 1 and phase 2. One could argue that drug development efforts might have been terminated at this early stage or more rigorously explored in early clinical development (and this may have been the case with such findings not published). In our opinion, if consistent neuropsychiatric adverse events are noticed in preclinical development and can be linked to the on-target pharmacology, the drug development program should be terminated as it is likely to cause concern later in development. If a decision is made to continue development of a particular compound to optimize the risk/benefit profile, early clinical studies should assess neuropsychiatric symptoms using well validated and sensitive clinical questionnaires coupled with experimental medicine approaches (including probing emotional or cognitive circuitry utilizing neuropsychological tasks and stress paradigms). These data should provide additional valuable information to make more informed decisions regarding progression of the candidate drug into phase 2 studies in patient populations.

There are some important observations that can be made from this review and should be highlighted. First, the mood related neuropsychiatric adverse events were more common with classes of drugs that reduced dopamine transmission directly or indirectly (i.e., the CB_1 and D_1/D_5 receptor antagonists, rimonabant, and ecopipam, respectively). On the other hand drugs that are known to increase monoamine neurotransmission directly (i.e., the monoamine reuptake inhibitors including sibutramine, buproprion, and tesofensine) tended to have positive or minimal effects on mood and anxiety symptoms. These observations suggest that a reduction in dopamine neurotransmission within the limbic areas could be a predictor of mood related psychiatric adverse events. Second, most of the studies do not appear to have used sensitive and validated clinical questionnaires or cognitive tests to probe neuropsychiatric adverse events, particularly in the early phase I/II studies. The failure to assess these adverse events more comprehensively may have underestimated potential risks.

Obesity has largely been categorized by many as a "risk" or "syndrome" rather than a "disease" and this raises the question about whether it is right that the safety requirements should be set higher than for other clinical indications. Obesity is a risk factor for metabolic syndrome, which can lead to cardiovascular disease and diabetes. Obesity is also associated with high prevalence of psychiatric comorbidities including anxiety and depression. Given the associated risks, one could argue that the risk/benefit is comparable to some of the other diseases where safety requirements for drugs may be lower. On the other hand, with antiobesity drugs, there is likely to be a certain amount of cosmetic use even with tight regulations and given that the medical benefits may not be immediately apparent (unlike many other diseases), weighing safety against likely long-term medical benefits can be challenging. However, regardless of the label (i.e., whether obesity is considered a risk or a disease), the adverse events caused by any central acting drug, particularly anxiety, depression, and suicidality should be alarming, in the context of chronic treatment. While there is a need to develop effective antiobesity drugs with long-term efficacy, patient safety is a paramount factor and hence the safety requirements should be set high.

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Authors of this article are employees of GlaxoSmithKline Pharmaceuticals and are directly involved in the development of antiobesity drugs. There are no published data on neuropsychiatric adverse events of centrally acting obesity drugs developed by GSK and hence their data are not referenced in this review.

Conflict of Interests

The authors have no conflict of interest.

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