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$GABA_B$ Receptors, Schizophrenia and Sleep Dysfunction:

A Review of the Relationship and its Potential Clinical and Therapeutic Implications

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Abstract

Evidence for an intrinsic relationship between sleep, cognition and the symptomatic manifestations of schizophrenia is accumulating. This review presents evidence for the possible utility of $GABA_B$ receptor agonists for the treatment of subjective and objective sleep abnormalities related to schizophrenia.

At the phenotypic level, sleep disturbance occurs in 16–30% of patients with schizophrenia and is related to reduced quality of life and poor coping skills. On the neurophysiological level, studies suggest that sleep deficits reflect a core component of schizophrenia. Specifically, slow-wave sleep deficits, which are inversely correlated with cognition scores, are seen. Moreover, sleep plays an increasingly well documented role in memory consolidation in schizophrenia. Correlations of slow-wave sleep deficits with impaired reaction time and declarative memory have also been reported. Thus, both behavioural insomnia and sleep architecture are critical therapeutic targets in patients with schizophrenia. However, long-term treatment with antipsychotics often results in residual sleep dysfunction and does not improve slow-wave sleep, and adjunctive $GABA_A$ receptor modulators, such as benzodiazepines and zolpidem, can impair sleep architecture and cognition in schizophrenia.

$GABA_B$ receptor agonists have therapeutic potential in schizophrenia. These agents have minimal effect on rapid eye movement sleep while increasing slow-wave sleep. Preclinical associations with increased expression of genes related to slow-wave sleep production and circadian rhythm function have also been reported. $GABA_B$ receptor deficits result in a sustained hyperdopaminergic state and can be reversed by a $GABA_B$ receptor agonist. Genetic, postmortem and electrophysiological studies also associate $GABA_B$ receptors with schizophrenia.

While studies thus far have not shown significant effects, prior focus on the use of $GABA_B$ receptor agonists has been on the positive symptoms of schizophrenia, with minimal investigation of $GABA_B$ receptor agonists such as baclofen or γ-hydroxybutyric acid and their effects on sleep architecture, cognition and negative symptoms in patients with schizophrenia. Further study is needed.

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1. Insomnia Related to Schizophrenia

Schizophrenia is a severe disorder associated with a broad range of symptomatic and neuropsychological disturbances. Disturbances of specific neurotransmitter systems, particularly dopamine,[1] glutamate[2] and GABA,[3] may be the proximate cause of symptoms and neurocognitive deficits. At present, all approved drugs for schizophrenia function primarily by modulating neurotransmission at dopamine D_2 receptors. There is a strong theoretical basis for intervention via glutamatergic and GABAergic mechanisms as well, and investigations of metabotropic glutamate receptor (mGluR2/3) agonists,[4] NMDA-modulating agents such as D-serine[5] or glycine,[6] and non-benzodiazepine $GABA_A$-receptor modulating agents[7] are ongoing. Optimal treatment for schizophrenia may, in time, involve multiple medications targeting specific aspects of the disorder.

D_2 receptor antagonists are primarily effective in the treatment of the positive symptoms of schizophrenia, such as delusions and hallucinations. Often, however, it is the other, less dramatic symptoms that are most disabling. These symptoms can include profound sleep disturbances, which have been recognized in psychotic disorders at least since Kraepelin,[8] and evidence has begun to accumulate for an intrinsic relationship between sleep, cognition and the symptomatic manifestations of schizophrenia. Antipsychotics and sedative hypnotics are only partially effective in treating insomnia related to schizophrenia, and it is likely that medications modulating other receptors will be needed.

This review presents evidence for a $GABA_B$ receptor agonist being potentially useful in schizophrenia and insomnia related to schizophrenia. The rationale for this review is 2-fold: first, sleep dysfunction is an important and overlooked aspect of schizophrenia, intrinsically linked to cognitive and functional impairments and, second, $GABA_B$ receptors regulate dopaminergic and glutamatergic systems *in vivo*, suggesting that agents that affect the $GABA_B$ receptor may be therapeutically beneficial in schizophrenia.

MEDLINE was searched up to May 2008 using the key words ‘schizophrenia, sleep, $GABA_B$’ for all English-language articles published that describe sleep dysfunction in schizophrenia, as well as the relationship of the $GABA_B$ receptor to schizophrenia. In addition, we examined review articles for other reports of interest that may have been missed by our initial search.

1.1 Sleep Disorders and Schizophrenia

Insomnia related to schizophrenia[9] is defined as difficulty initiating or maintaining sleep, or nonrestorative sleep, for at least 1 month that is associated with daytime fatigue or impaired daytime functioning. It must cause functional impairment and not be better accounted for by another sleep disorder or be due to the direct physiological effects of a substance or a general medical condition. This definition is an inclusive one and does not consist only of decreased total time asleep. Inherent to this disorder is daytime fatigue, which can be mistaken for sedation or hypersomnia, and, as described in section 1.1.1, phenotypic hypersomnia often masks nonrestorative night-time sleep or impaired sleep architecture. Sleep dysfunction is manifest in schizophrenia at both the behavioural (phenotypic) and objective (neurophysiological) levels.

1.1.1 Phenotypic Level—At the phenotypic level, insomnia is a frequent symptom in schizophrenia independent of other aspects of psychosis.[10–12] For example, while baseline rates of sleep dysfunction were not reported, 16–30%of patients across treatment arms in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study reported insomnia and 24–31% reported hypersomnia.[13] Moreover, poor sleep quality has been correlated with reduced quality of life and poor coping skills.[12,14] Acute exacerbations of psychosis are associated with restless, agitated sleep,[15] with insomnia often serving as an early warning sign of clinical relapse.[16] Even among stable patients, in all illness phases, early and middle insomnia is common,[10] as is sleep-wake reversal.[17] It is clear that sleep disturbances in schizophrenia are more complex than just difficulty initiating sleep, which complicates a phenomenological description.

1.1.2 Neurophysiological Level—On the neurophysiological level, impaired sleep is associated with measurable, objective deficits in sleep architecture, sometimes even without apparent deficits in total sleep time.[18] In other words, nonrestorative sleep can occur in schizophrenia even without clear reductions in total time in bed. Although the literature is somewhat conflicting,[19,20] making definitive statements difficult, many studies have shown severe difficulties in sleep initiation, sleep efficiency, and stage II and stage III–IV (i.e. slow-wave sleep), as well as increased rapid eye movement (REM) density in patients tapered off antipsychotic agents.[20,21] Similar deficits have also been found in antipsychotic-naive, first-episode patients[22] and in patients maintained on antipsychotics,[23,24] suggesting that such deficits may reflect a core component of the disorder. In particular, patients with schizophrenia may show reduced time spent in the deepest stages of sleep,[18,25] potentially resulting in significant reductions in sleep quality,[26] although this finding may be related to antipsychotic withdrawal in some cases.[19] It is also possible that poor sleep may be related to symptomatic worsening,[21] as slow-wave sleep may be inversely correlated with Positive and Negative Syndrome Scale (PANSS) cognition scores. Sleep may also play a role in mortality and morbidity, as REM sleep abnormities have been linked to a higher rate of suicide in schizophrenia,[27] and low levels of slow-wave sleep may contribute to an increased risk of type 2 diabetes mellitus in normative populations.[28] Although the aetiology of sleep dysfunction in schizophrenia is unknown, both glutamatergic, acting through NMDA receptors,[29] and GABA systems,[30] as well as the serotonin system,[31] are known to play critical roles in sleep homeostasis.

1.1.3 Sleep, Memory and Learning—Sleep deficits in schizophrenia represent an important therapeutic target not only because insomnia impairs general performance, but also because sleep plays an increasingly well documented role in cognition, particularly with respect to the consolidation of memory.[32,33] Declarative and procedural memory consolidation have been shown to be associated with slow-wave[34] and stage II[35] sleep, respectively. Sleep-related learning deficits in schizophrenia have been demonstrated in multiple paradigms, including those that are specifically sensitive to sleep deprivation.[36] Stage IV sleep deficits are correlated with reduced reaction time in selective and sustained attention tasks,[37] and procedural learning and visual spatial memory are correlated with delta power in slow-wave sleep.[23,24] These studies demonstrate the importance of sleep

architecture, rather than just behavioural insomnia, as critical therapeutic targets in schizophrenia.

1.2 Current Therapeutic Approach

At present, sleep disturbances in schizophrenia are treated primarily with antipsychotics and/or adjunctive sedative-hypnotic medications. While somewhat effective at reducing behavioural disturbances, these medications rarely correct underlying polysomnographic disturbances, and thus do not restore normal brain physiology. Furthermore, they are often associated with a daytime 'hangover' effect, which can contribute significantly to poor global function. Finally, whereas some antipsychotics such as chlorpromazine and clozapine are highly sedating and thus have, as a side effect, the ability to ameliorate insomnia, other antipsychotics such as aripiprazole and ziprasidone are less sedating and may even be activating. A shift to use of a less sedating medication, therefore, may reveal previously masked sleep disturbances, necessitating new approaches.

1.2.1 Antipsychotics—Previous efforts to treat both subjective and objective sleep disturbance in schizophrenia with antipsychotics have had mixed success. Small studies have shown improvement in subjective sleep[38,39] and sleep quality[40] in patients switched to atypical antipsychotics. Nevertheless, as noted previously, a large proportion of patients in the CATIE study experienced sleep problems despite treatment with atypical antipsychotics, with no significant differences between treatment arms.[13]

Neurophysiological deficits related to sleep impairment may be improved acutely by atypical antipsychotics such as olanzapine and risperidone,[20,41,42] but nevertheless do not normalize. Furthermore, while multiple antipsychotics have been shown to be associated with at least short-term, small increases in slow-wave sleep in normative controls,[43] the long-term effects of antipsychotics on sleep architecture in schizophrenia are unclear. For example, in two longer studies of paliperidone and clozapine, stage II[39,44] and REM[39] sleep increased, but slow-wave sleep did not. A 4-week open-label trial of olanzapine[45] demonstrated improvement in slow-wave sleep, but in a recent cross-sectional study of quetiapine and risperidone,[46] slow-wave sleep was reduced in patients receiving these agents in comparison with an unmedicated first episode group. Moreover, a recent study using high-density EEG found reduced sleep spindle activity and reductions in EEG power throughout stage II–IV over the centroparietal areas in patients with schizophrenia medicated with various antipsychotics,[24] providing further evidence that antipsychoticsmay not normalize sleep architecture in the long term.

1.2.2 $GABA_A$ Receptor Modulators—$GABA_A$ receptor modulators, including benzodiazepines and newer non-benzodiazepine sedative hypnotics (e.g. zolpidem and zopiclone), are the mainstay of insomnia treatment in schizophrenia. These compounds improve insomnia primarily by decreasing sleep latency and episodes of brief nocturnal awakenings. However, even within normative populations they do not increase (and may decrease) slow-wave sleep and overall sleep quality.[47,48] Furthermore, a recent meta-analysis of the use of benzodiazepines in patients with schizophrenia[49] was equivocal with regard to sedative effects, and found minimal evidence supporting behavioural

improvements. In schizophrenia, benzodiazepines and zopiclone have been found to impair sleep architecture[50] and cognition.[51]

1.2.3 Melatonin and Modafinil—Melatonin may be useful for improving subjective sleep in schizophrenia,[52,53] but as with benzodiazepines, melatonin does not, in general, improve slow-wave sleep parameters. More recently, modafinil has been studied as a potential cognitive enhancer and as an agent for reducing antipsychotic-associated fatigue. While initial open-label studies were promising,[54,55] double-blind studies of the effects of therapy on fatigue,[56] executive functions[57] and negative symptoms and cognition[58] have shown no difference between adjunctive modafinil and placebo.

1.3 Effects of $GABA_B$ Receptor Agonists on Sleep Architecture

While there have been few trials of $GABA_B$ receptor agonists in schizophrenia and insomnia, several studies in animal and normative populations and informative pathological conditions support a potential therapeutic role.

First, GABA is linked to sleep homeostasis in several animal populations. $GABA_A$ receptor agonists and modulators (such as benzodiazepines) can decrease slow-wave and REM sleep in rats.[30] $GABA_B$ receptor agonists, however, *minimally impact* REM sleep while increasing slow-wave sleep,[59] leading to increased expression of genes[30] related to slow-wave sleep production and circadian rhythm function.[60] Conversely, $GABA_B$ receptor antagonists decrease overall sleep in rats, with particularly detrimental effects on slow-wave sleep.[61] Although $GABA_B$ receptor agonists have been associated with impaired cognition,[62] and $GABA_B$ receptor antagonists have been associated with improved cognition in rats, this effect might actually be due to $GABA_C$ receptor antagonist activity[61] and not mediated through $GABA_B$ receptors.

Second, human studies with the $GABA_B$ receptor agonist γ-hydroxybutyric acid (GHB; sodium oxybate) show improvements in sleep architecture deficits and subjective sleep. Dose-dependent improvements in subjective sleep, daytime sleepiness, slow-wave sleep, delta power, sleep efficiency and REM sleep efficiency have been shown in narcolepsy,[63–65] with similar improvements seen in patients with fibromyalgia[66] and sleep apnoea.[67] Although no controlled studies have directly evaluated the effects of GHB on cognition in either narcolepsy or fibromyalgia, a recent case report associated GHB with an improvement in neurocognitive functioning in an 8-year-old boy with bithalamic lesions.[68]

2. $GABA_B$ Receptors and Schizophrenia

In addition to a potential interaction between schizophrenia, sleep and cognition, accumulating evidence links schizophrenia directly with $GABA_B$ receptor deficits. GABA is the main inhibitory neurotransmitter in the brain, with extensive representation in most brain regions. The $GABA_B$ receptor is a G-protein-coupled metabotropic receptor that is negatively coupled to adenylyl cyclase, inactivates voltage-dependent calcium channels and decreases inositol triphosphate production.[69]

2.1 Interactions with Dopamine

The involvement of GABA in schizophrenia was first proposed by Roberts in 1972,[70] hypothesizing a GABA imbalance. More recent studies have emphasized a deficit in GABA interneurons.[71,72] These neurons receive dopaminergic input from the midbrain and express multiple subtypes of dopamine receptors;[73,74] they also play a role in working memory.[75]

$GABA_B$ receptors are localized on presynaptic dopaminergic terminals[76] and are involved in inhibiting dopamine release and modulating glutaminergic regulation of dopamine.[3,77] $GABA_B$ receptor-deficient mice have been shown to be in a sustained hyperdopaminergic state, resulting in hyperlocomotive behaviour.[3] Moreover, in a linkage to the glutamate hypofunction model of psychosis,[78] disinhibition of glutamate modulation of mesolimbic dopamine and GABA transmission in the ventral tegmental area can be reversed by a $GABA_B$ receptor agonist.[79] A recent, preclinical study[80] suggests that the aetiology involved may be potentiation of NMDA-stimulated GABA release and presynaptic $GABA_B$ receptor activation.

2.2 Genetic, Postmortem and Electrophysiological Links with Schizophrenia

Although relatively few postmortem studies have been conducted, $GABA_B$ receptor protein has been found to be decreased in the pyramidal cells of the entorhinal cortex and layer 5 pyramidal cells in the inferior temporal cortex of postmortem brains in schizophrenia.[81] Similar findings have been reported for $GABA_B$ receptor protein in the hippocampus. One of the most consistent postmortem findings in schizophrenia is a reduction in parvalbumin and glutamic acid decarboxylase-67 (GAD67) expression in parvalbumin-positive GABAergic interneurons.[82] In the frontal cortex, deficits have been demonstrated particularly in chandelier neurons, which may give rise to frontal γ activity. It has been proposed, therefore, that treatment with GABAergic agents may reverse frontal and GABAergic deficits in schizophrenia, leading to restoration of frontal function.[83] In striatal slices, the effects of the actions of glycine transport inhibitors on GABA are mediated particularly by $GABA_B$ receptors located on presynaptic dopamine terminals.[84] This suggests that GABAB receptor agonists or allosteric modulators may also be therapeutically beneficial.

Genetic and electrophysiological studies have also related $GABA_B$ receptors and schizophrenia. The *$GABA_BR1$* gene has been associated with schizophrenia in at least one study involving Caucasians,[85] although other studies involving Japanese[86] and Han Chinese[87] populations have been negative. GAD65 (a GABA synthesizing enzyme) knockout mice show prepulse inhibition deficits.[88] Furthermore, the $GABA_B$ receptor agonist baclofen, administered intraperitoneally, has been shown to reverse both dizocilpine-induced pre-pulse inhibition disruption and spontaneous deficits in DBA/2 mice, similar to clozapine and haloperidol,[89,90] indicative of potential therapeutic benefit in schizophrenia. Moreover, the effects of baclofen were prevented by pretreatment with a $GABA_B$ receptor antagonist. Finally, DBA/2 mice were found to have reduced $GABA_B$ expression in both prefrontal cortex and hippocampus, suggesting that the schizophrenia-like phenotype of these mice may be due, in part, to disturbances in GABAergic phenomenology.

2.3 Prior Experience with $GABA_B$ Receptor Agonists and Modulators in Schizophrenia

2.3.1 Baclofen—To date, the only available $GABA_B$ receptor agonists approved for human use are baclofen and GHB. Baclofen is indicated for treatment of spasticity, due primarily to effects at the spinal cord level. Baclofen has poor liposolubility and does not cross the blood-brain barrier efficiently. Consequently, even at high doses, oral baclofen reaches relatively low concentrations in the cerebrospinal fluid,[91] necessitating intrathecal use. There is little evidence to support its use in cerebral spasticity.[92]

As noted in section 2.2, in animal models, baclofen has effects similar to clozapine on dizocilpine-induced and spontaneous pre-pulse inhibition deficits in mice.[89,90] Baclofen is also associated with hallucinations on abrupt withdrawal.[91] Despite this preclinical evidence, schizophrenia treatment trials with baclofen have been disappointing. Baclofen was studied in multiple trials in the 1970s (see review by Garbutt and Van Kammen[93]). An initial open-label trial of 13 patients was promising;[94] however, subsequent randomized, double-blind, placebo-controlled trials failed to confirm these effects, with only 14 of 90 patients improved and 36 worsened.[93] In contrast, baclofen was not associated with clinical deterioration in a series of trials for tardive dyskinesia.[95–97] Moreover, in recent case reports,[98,99] baclofen was effective in suppressing substance abuse in two psychotic patients.

In published studies,[93] baclofen was typically used as monotherapy, and specific effects on electrophysiology, sleep architecture, cognition and negative symptoms were not reported. However, baclofen is not definitively associated with increases in slow-wave sleep, even in non-schizophrenia populations,[100,101] and as noted above, it does not cross the blood-brain barrier efficiently. It is therefore unclear whether baclofen would be specifically useful in insomnia related to schizophrenia.

2.3.2 γ-Hydroxybutyric Acid—A growing preclinical evidence base also links GHB with dopamine modulation. GHB is thought to act directly as a neurotransmitter but also interacts with dopamine via the GHB receptor and with the $GABA_B$ receptor after conversion to extracellular GABA.[102] Dopamine modulation is mediated mainly through the $GABA_B$ receptor,[59] as $GABA_{B1}$ knockout mice do not exhibit the same behavioural response to GHB administration as wild-type mice. Experimentally, GHB lowers the output of dopamine in the ventral tegmental area in a dose-dependent fashion.[103] There is evidence that the GHB receptor might directly interact with the dopaminergic system, as the density of high-affinity GHB receptors is particularly high in dopaminergic structures.[104] Moreover, benzamide antipsychotics, such as amisulpride, are agonists at the GHB receptor.[105] Despite also being hydrophilic, GHB may have an advantage over baclofen in achieving meaningful CNS concentrations, as there is evidence for carrier-mediated transport across the blood-brain barrier.[106]

We are aware of three previous trials of GHB in schizophrenia.[107–109] In the earliest trial, which was open label,[107] improvement was noted, especially in patients with insomnia or negative symptoms. Dosage varied from 1 to 8 g/day, and although formal ratings were not given, 70% of patients with disorganized schizophrenia and 60% of patients with catatonic schizophrenia reportedly improved.

Subsequently, two small, controlled trials[108,109] did not show an overall benefit. We noted multiple limitations in these controlled trials, including: (1) requirement of cumbersome dosage patterns (up to six times daily) that could have led to incomplete compliance; (2) lack of objective measures of subjective sleep or sleep architecture; (3) lack of objective cognitive testing; (4) use of GHB as monotherapy or only in conjunction with low-dose antipsychotics (e.g. fluphenazine 5 mg/day); (5) short trial duration (<4 weeks); (6) relatively low overall night-time dose of GHB; and (7) a heterogeneous, small sample. We are in the preliminary stages of a proof-of-concept trial of GHB in insomnia related to schizophrenia, with both subjective and objective measures of sleep !as outcome measures (see clinicaltrials.gov – NCT00594256). As opposed to prior studies, GHB will be administered only at night, and both night-time sleep and daytime alertness will be monitored. Furthermore, GHB will be used as adjunctive therapy to ongoing antipsychotic treatment. A potential problem with GHB is its short elimination half-life, necessitating twice-nightly administration, possibly limiting its use to an inpatient unit for practical purposes.

2.3.3 $GABA_B$ Receptor Antagonists and Novel $GABA_B$ Receptor Modulators—

In addition to $GABA_B$ receptor agonists, both $GABA_B$ receptor antagonists and receptor modulators are in the early stages of development. Multiple preclinical studies have reported a role for $GABA_B$ receptor antagonists in the treatment of cognitive dysfunction. A study reported improvements in learning and memory retention in a rat model of absence epilepsy.[110] More recent studies have demonstrated that the $GABA_B$ receptor antagonist SGS742 improves spatial memory, an effect attributed to reduced protein binding to the cyclic adenosine monophosphate response element in the hippocampus.[111] Others have demonstrated that $GABA_B$ receptor blockade may enhance cognitive task performance by activating hippocampal θ and γ rhythms in behaving rats.[112] However, as noted in section 1.3, $GABA_B$ receptor antagonists decrease overall sleep in rats, with particularly detrimental effects on slow-wave sleep,[61] and would therefore probably be unhelpful in the treatment of insomnia associated with schizophrenia.

$GABA_B$ receptor modulators, such asGS39783, CGP7930 and CGP13501,[113] are being increasingly studied. Following up on recent case reports[98,99] of the effectiveness of baclofen in treating substance abuse, preclinical trials have demonstrated reduced cocaine self-administration after treatment with positive allosteric modulators of the $GABA_B$ receptor.[114] These medications have not been tested in a model of psychosis and, moreover, appear to be less sedating; for these reasons, they hold less promise as a potential treatment for insomnia associated with schizophrenia.

3. Future Directions and Conclusion

Evidence for an intrinsic relationship between sleep, cognition and the symptomatic manifestations of schizophrenia is accumulating. Insomnia remains a significant problem for approximately 25% of patients with schizophrenia, and sleep disorders may be intrinsically related to cognitive deficits in schizophrenia. Currently available treatment does little to improve slow-wave sleep. Furthermore, adjunctive $GABA_A$ receptor modulators such as benzodiazepines, although widely used as sleep aids in schizophrenia, can impair, rather

than correct, sleep architecture and cognition. In contrast, $GABA_B$ receptor agonists may have minimal impact on REM sleep while increasing slow-wave sleep. While past studies of $GABA_B$ receptor agonists in schizophrenia have not shown significant effects, prior focus has been on positive symptoms, and there has been minimal investigation of the effects of these agents on sleep architecture, cognition and negative symptoms in schizophrenia. Further study is therefore needed, particularly as novel $GABA_B$ receptor modulators become clinically available.

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