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# Will the Treatment Protocols for Schizophrenia Be Changing Soon?

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## Abstract

In recent decades the understanding of the core physiology giving rise to schizophrenia has advanced markedly. Current pharmacological interventions fail to target the core problems in schizophrenia. Several important outcome studies call into question whether current medications actually make long term outcomes worse. These new studies follow the recognized negative side effect of anti-psychotic drugs. The implication of these findings for social workers who work with the seriously mentally ill are discussed. Alternatives to current pharmacological treatments which are more targeted toward the core physiology of schizophrenia are reviewed.


Key Words: Schizophrenia, Atypicals, Fast-spiking-interneurons, NMDAR, Anti-psychotics, N-acetyl-cysteine, omega-3s

# WILL THE TREATMENT PROTOCOLS FOR SCHIZOPHRENIA BE CHANGING SOON?

The mainstay for treatment of schizophrenia has been anti-psychotic drugs since their introduction in the 1950s. Initially, only the first generation anti-psychotic drugs were available, but since the 1980s, the new atypical anti-psychotics were introduced (Harrow, Grossman, Jobe, & Herbener, 2005). The evaluation of these drugs to date has relied on short-term efficacy studies of eight weeks. The question of whether these drugs would decrease relapse has been addressed through studies following clients for one to two years. These studies have been relatively consistent in finding less relapse and hospital readmission when patients are maintained on drugs (Leucht et al., 2012). However, several more recent studies had longer follow-up and evaluated global functioning as opposed to only relapse and readmission. The longer follow-up studies found worse outcomes in the medicated patients. Continuing revelations regarding the side effects of antipsychotic drugs have raised further questions regarding the best treatments for those with schizophrenia. More crucially, identification of the core brain dysfunction in schizophrenia reveals that anti-psychotics fail to target the core dysfunction. This paper will review the findings from longer investigations as well as the studies of alternative treatments for schizophrenia which do target the core brain dysfunctions and have far fewer negative side effects.

## Studies with Longer Follow-Up

Wunderink, Nieboer, Wiersma, Sytema, and Nienhuis (2013) examined both the short and long term efficacy of antipsychotic treatment for first episode schizophrenia. Wunderink et al. acknowledged that the literature suggested that for the first two years after the emergence of psychosis, those who continue on medications have lower rate of relapse than those who

discontinue their medications (see Leucht et al., 2012). However, Wunderink et al. wanted to examine how medications influence the longer term outcomes. They recruited individuals, for an initial two year study, who had maintained low levels of symptoms for six months. (In terms of representativeness of the sample, about half of the eligible population agreed to participate in the study.) The recruited 128 subjects were then randomly assigned to an 18 month discontinuation of their antipsychotic drug or maintenance on their drug. After study completion at two years, control of patient treatment was up to the discretion of physicians in the community. Five years after the completion date, Wunderink et al. followed up on those patients who had been in the original two year study.

At seven year follow-up, Wunderink et al. were able to locate 80.5% of the original participants: 52 from the discontinuation arm and 51 from the maintenance arm. Only eight of the patients from the discontinuation arm remained unmedicated throughout the seven years. Thus, many in the discontinuation group did later receive meds. What was different between the groups was that the drug discontinuation group received significantly lower drug dosages than those in the drug maintained arm. In terms of outcome at year seven, the percentage experiencing at least one relapse did not differ statistically between the groups (61.5% in discontinuation arm versus 68.8% in the continue-with -medication arm), nor did the groups differ on mean number of relapses during the seven year period (1.13 versus 1.35). Where the differences showed up is in when the relapses occurred. The relapses for the drug discontinuation were more likely to have occurred during the first two years of the follow-up interval, replicating what others had found. But where the dramatic, and possibly the more important differences lie, was in the percentages of functional recovery between the two groups. 46.2% of those in the discontinuation arm achieved functional recovery versus 19.6% in the

drug maintenance arm. Thus, more of the clients in the anti-psychotic discontinuation group were able to work and achieve meaningful relationships with others than those who had been more continuously medicated.

It should be noted that Wunderink et al. (2013) is not the only study finding worse outcomes in those who are medicated to a greater extent. A study in Australia assessed the impact of a program of enhanced treatment for decreasing relapse. While at one year, relapse was reduced in the enhanced treatment arm compared to the control group, at 2.5 year follow-up differences between the groups were no longer apparent on relapse. Surprisingly, the enhanced treatment group displayed worse social and cognitive functioning which statistical analysis suggested was mediated through enhanced medication compliance (Gleeson et al., 2013). In another study, Johnstone, Macmillan, Frith, Benn, and Crow (1990) also found that after a first episode, those who were unmedicated exhibited better functional outcomes than those who were medicated. Forty percent of those who were not on medication remained well throughout the two-year follow-up.

Unfortunately, studies comparing those who do and do not remain on antipsychotic drugs often confound patient characteristics with the impact of medications. Harrow, Jobe, and Faull (2012) followed their patients over 20 years. 15% of the research participants were always on meds whereas 24% were never on meds. Those who eschewed pharmacological treatment were higher functioning as evidenced by higher scores on IQ tests and on tests of abstract reasoning. The outcomes for those in the Harrow et al. study who were unmedicated were much better. 87% achieved functional recovery in contrast to only 17% of the medicated group achieving any period of functional recovery. Relapse rates were higher in the medicated group.

The better outcomes for those who are unmedicated are consistent with the results of studies by the World Health Organization (WHO). The WHO studies were conducted in a wide variety of countries yielding the consistent finding that those with first-episode schizophrenia achieve superior outcomes in developing countries (Nigeria, India and Columbia) compared to developed nations (Japan, Europe and the United States), with good outcome of 63% in developing countries versus 37% in developed countries. The researcher did confirm that patients with first episode were less likely to be medicated in developing countries (16% versus 61%) (Jablensky et al., 1992, p.64). (It should be noted that across cultures, those with schizophrenia were consistent in the symptoms that were manifested; thus, the same types of persons were identified across settings.) Of course, many factors differentiate developing versus developed countries: the complexity of the society, family cohesion, and access to medications. However, the consistency in the findings, with the percentage of patients only experiencing one episode being higher in 80% of the developing countries compared to developed countries (p.63), yields the conclusion that either medications fail to lead to better outcomes or at least cannot compensate for deleterious cultural factors. (It should be noted that the one location in developing countries with more negative outcomes also was distinguished by having a higher level of medicating.) The diversity of developing-world and developed cultures suggests that better outcome for less developed societies can be expected regardless of culture context.

Perhaps inconsistent with better outcomes for the non-medicated, several meta-analyses addressed the question of whether early treatment in the course of the illness with medications of those with schizophrenia influences the frequency and duration of psychotic episodes. Analyses by Marshall et al., (2005) and Perkins, Gu, Boteva, and Lieberman (2005)

concluded that early treatment is associated with better outcome. However, those delaying treatment exhibited more severe negative symptoms (that is cognitive dysfunction, lack of motivation, and flatter affect). Cognitive deficits, a component of negative symptoms are themselves associated with worse outcome (Brekke, Hoe, long, & Green, 2007; Green & Nuechterlein, 1999). In some studies the relationship between duration of untreated symptoms and outcome disappears after controlling for negative symptoms and Marhall et al. report that duration of untreated psychosis only accounted for 13% of the variance. A recent meta-analytic review by Bola (2006) found little evidence for better outcome with early treatment.

While the studies finding better outcome in those persons with schizophrenia for whom medication was discontinued, there is also the question of whether psychosis will spontaneously remit in some persons. Bola and colleagues were able to locate studies of those with first-episode schizophrenia who were assigned to a delay medicating arm of treatment. Across studies, between 27-43% of those assigned to the minimal medications group remained unmedicated over a two to three year period (Bola, Kao, & Soydan, 2012; Bola, Lehtinen, Culberg & Ciompi, 2009). The expectation of resolution of psychosis in as much as 43% is consistent with the findings of the WHO which suggested good outcome in 63% of persons in countries in which very few were medicated and with Bola and Mosher's (2002) review of studies examining recovery before the advent of medications finding that 50% achieved functional recovery.

McGorry, Alvarez-Jimenez, and Killackey (2013) contributed editorial commentary on the Wunderink et al. recently published study. McGorry et al. suggested that tolerating initial exacerbation of symptoms with drug discontinuation "may be a price worth paying for better

longer-term functional recovery". They further added that "an early guided discontinuation strategy would find the small subset of patients who can recover with no anti-psychotic medications--those whose first episode will also prove to be their last." The Wunderink et al. study is under discussion by many. Tom Insel, Director the National Institute of Mental Health, in his "Director's blog" of August 28, 2013 discussed the Wunderink et al. study, acknowledging the failings with the current pharmacological approaches to schizophrenia.

**Treatment with Antipsychotics Is Toxic**

Perhaps the worst indictment of antipsychotic drugs is that they have been proven to reduce cortex volume in primates (macaque monkeys) on what is a standard dose for humans taken over a 27 month period (Dorph-Petersen et al., 2005; Konopaske et al., 2007; Konopaske et al., 2008). Not only was there a reduction in cortex volume but also the number of supporting cells (called glia) was significantly reduced as well (Konopaske et al., 2008). The glial cell reduction is notable because these cells release growth factors which are vital to maintain the health of the brain (Schwartz & Schechter, 2011; Ziv & Schwartz, 2008). The primate results are consistent with the results of treatment with antipsychotics in humans. Ho, Andreasen, Ziebell, Pierson, and Magnotta (2011) found significant reduction in cortex volumes in humans treated with anti-dopamine drugs for both the old neuroleptics and newer atypicals. The degree of cortex volume reduction was correlated with drug dosage.

The finding of brain cortex reduction followed other findings which questioned the wisdom of antipsychotics for reducing psychosis over the long term. Psychotic symptoms are produced by excessive release of dopamine in the Nucleus Accumbens (Grace, 2012; Howes & Kapur, 2009). Antipsychotic medications occupy the D2 receptors for dopamine in the N. Accumbens and block the impact of the dopamine on the post-synaptic neuron. However, the

system as a whole adjusts, yielding a phenomenon called dopamine super-sensitivity: the expression of D2 receptors increases to compensate for the blockage (Grace, 2012). Additionally, the receptors for dopamine are of a high affinity variety as opposed to the lower affinity receptors observed in a naïve animal (Seeman et al., 2005). Thus, should a patient discontinue his/her antipsychotic medication, the psychotic symptoms will be far more extreme than the symptoms in a drug naïve patient. In fact, when patients discontinue medication the relapse rates during the first six-ten months are much higher than during later periods (Harrow & Jobe, 2013). The dopamine super-sensitivity might well explain why even for those who are compliant with their medications, relapse rates during a 1 to 2 year period vary from 18-55% (Samaha, Seeman, Stewart, Rajabi, & Kapur, 2007).

Unfortunately, the impact of antipsychotic treatment on the brain mirrors all of the other quite terrible effects of antipsychotic treatment on other organ systems of the body. The atypical antipsychotics are notorious for causing severe obesity, dyslipidemia, and type 2 diabetes (Pramyothin & Khaodhiar, 2010; van Os & Kapur, 2009). Because the effect of dopamine is blocked, prolactin levels rise and osteoporosis occurs (Calarge, Zimmerman, Xia, Kuperman, & Schiechte, 2010). In fact, the disparity in longevity between those with schizophrenia and others has increased since the introduction of the atypical antipsychotics (van Os & Kapur, 2009). Acutely, the newer atypicals are known for provoking cardiac arrhythmias potentially resulting in sudden death (Haddad & Anderson, 2002). Dopamine has been characterized as a neurotransmitter which increases motivation and drive. Blocking this neurotransmitter induces dysphoria and motivational impairment (van Os & Howe, 2009). Finally, antipsychotics are also associated with movement problems similar to those observed in Parkinson's disease, which are present with both older and newer drugs (Casey et al., 2006).

## Targeting the Actual Cause of Schizophrenia

### *The familiar dopamine hypothesis of schizophrenia*

The theory that the symptoms of psychosis are caused by excessive release of dopamine was promulgated decades ago. Drugs (cocaine and amphetamines) which increase dopamine release in the N. Accumbens (sometimes called "ventral striatum") reliably produce psychosis. With the advent of better imaging techniques it is possible to confirm the theory. Those with schizophrenia have been given radiolabeld l-dopa, the precursor to dopamine. The radiolabel makes it possible to quantify (to see) the amount of dopamine in the Nucleus Accumbens. Unmedicated persons with schizophrenics do have more dopamine in their Nucleui Accumbens than normal controls and the level of dopamine correlates with psychotic symptoms. It is also possible to observe the release of dopamine. Radioactive substances that occupy D2 receptors are given. If the radioactive tag disappears, the assumption is that released dopamine has displaced the label. Those with schizophrenia do display less radioactive label in the N. Accumbens. Again, the level of dopamine release correlates with psychotic symptoms (Grace, 2012; Howe & Kapur, 2009).

The display of psychotic symptoms is not unique to schizophrenia. As stated above, dopamine agonist drugs can induce psychosis. Studies such as the ones conducted on persons diagnosed with schizophrenia confirm that excess dopamine in the Nucleus Accumbens is the cause of the psychotic symptoms. For those with schizophrenia, the next question is "why do they release more dopamine in the Nucleus Accumbens?" Attempts to identify differences in the dopaminergic system have failed to reveal differences (Grace, 2012) and some of the gene candidates identified as risk factors for schizophrenia are not related to dopamine function (Howes & Kapur, 2009). A variety of findings have converged on differences in the cells that

control the dopamine system: the parvalbumin positive (PV +), GABA producing, fast-spiking, interneurons (Curley et al., 2011).

### *What Defines Schizophrenia?*

The fast-spiking, PV+, GABA producing interneurons, which control dopamine release, also produce characteristic electrical activity called gamma oscillation (Bartos, Vida, & Jonas, 2007; Grace, 2012; Labrie & Roder, 2010). According to Powell, Sejnowski, and Behrens (2012, p. 3) "alterations in brain oscillatory activity is the hallmark of schizophrenia pathophysiology" and according to Steulet et al. (2010, p. 2547) referring to schizophrenia, "abnormality in synchronized neuronal activity driven by fast-spiking interneurons is a core feature of this disorder". Gamma oscillations are associated with the capacity to form a coherent perception after detecting various features through the sensory systems; encoding of information; and the recall and storage of information. Gamma frequency reduction as well as performance deficits in a wide range of tasks have been found in persons with schizophrenia (Green & Nuechterlein, 1999; Volk & Lewis, 2013). More specifically, those with schizophrenia fail to generate gamma oscillations when performing particular cognitive tasks. Those with schizophrenia not only show performance decrements on short term memory tasks, but they have difficulty detecting motion (Kantrowitz & Javitt, 2010), distinguishing pure tones (Deo et al., 2013), distinguishing prosodic changes, and understanding the meaning of words when they are used in a metaphorical sense (Kantrowitz & Javitt, 2010), and recognizing sarcasm (Kantrowitz, Hoptman, Leitman, Silipo, & Javitt, 2013). Indeed, as a group, those with schizophrenia score one standard deviation below average on measures of cognitive function (van Os & Kapur, 2009). Elvevag and Goldberg (2000) argue that negative symptoms

(lethargy and lack of motivation) and cognitive deficits better distinguish those with schizophrenia than hallucinations and delusions.

It is known that cognitive deficits are frequently present long before the emergence of psychosis in those who will be later diagnosed as schizophrenic. Observers of home movies of children at preschool age can identify many of those individuals who later develop schizophrenia because of abnormal movements of their upper limbs (Walker, Lewine, & Neumann, 1996). Tardiness in meeting developmental milestones is a predictive factor in the emergence of later psychosis (Sorensen et al., 2010). Thompson, Nelson, and Yung (2011) have described a constellation of traits which identify children who are at high risk for developing schizophrenia. In fact in a two and half year period, 65% of these children developed overt psychosis in the Thompson et al study.

### *What Is Not the Defining Feature of Schizophrenia*

Population studies have found that as much as 8% of the general population report hearing voices with about 4% experiencing distress attributable to these events (Howes & Kapur, 2009). Thus, hearing voices is not unique to schizophrenia. Heins et al. (2011) identified early stress in the backgrounds in those who later manifest auditory hallucinations. Trauma predicted hallucinations but not cognitive deficits and lack of motivation. The persons in Heins et al. study would probably not meet criteria for schizophrenia as the diagnosis requires social and occupation dysfunction more closely associated with negative rather than positive symptoms (Milev, Ho, Arndt, & Andreasen, 2005). Thus, hearing voices fails to distinguish those with schizophrenia.

## *Parvalbumin Positive GABAnergic Interneurons*

Dysfunction of GABA, fast-spiking, interneurons in those with schizophrenia is supported by many findings. Autopsied brains of those with diagnosed schizophrenia are deficient in the precursor to enzyme (GAD67) which produces the neurotransmitter GABA in PV + interneurons; there are fewer synaptic contacts of the GABA interneurons . Reduced levels of PV precursors have also been noted in cortical inhibitory neurons (Volk & Lewis, 2013).

***NMDA hypofunction disrupts PV+ GABAnergic interneurons.*** The drive on GABA producing interneurons comes from activity at an NMDA receptor for glutamate on the membrane of the GABA producing interneuron (Snyder & Goa, 2013). The integrity of signaling through the NR2A subunit of the NMDA receptors is required to maintain levels of GAD67 and PV in fast-spiking GABA interneurons (Kinney et al., 2006). Those with schizophrenia exhibit lower levels of the NR2A subunit (Bitanhihirwe, Lim, Kelley, Kaneko, & Woo, 2009).

Psychiatry acknowledges that the category of schizophrenia probably contains a wide diversity of pathways to symptoms and dysfunction of the GABA interneurons (van Os & Kapur, 2009) with some pathways probably being more prevalent in particular ethnic groups. A plethora of pathways to GABA interneuron dysfunction have been identified, and according to Steullet et al. (2006, p. 816), referring to schizophrenia, “Because of the heterogenetiy of illness, it is likely that several different defects cause hypofunction of the NMDA receptors in different subgroups of schizophrenic patients.” Some of these pathways are consistent with the risk factors that have been identified for schizophrenia.

***Changes in the auxiliary proteins that augment NMDAR signaling.*** The NMDAR receptor is comprised of several subunits. One subunit responds to glutamate but only when the

other subunit has either glycine or d-serine bound to it. Occupancy of NMDAR receptors in the hippocampus have been measured in vivo in drug free persons with schizophrenia, showing less receptor occupancy than normal controls. Those with schizophrenia exhibit lower levels of endogenous ligands (d-serine) in plasma, and d-serine levels are inversely correlated with positive and negative symptoms. Genetic changes for proteins involved in d-serine metabolism are associated with the risk for schizophrenia (Labrie & Roder, 2010).

***Potential Causes of NMDAR Signaling Alterations***

***Genetic factors.*** Genetic changes in proteins for signal delivery at the NMDA receptor have been repeatedly identified as risk factors for schizophrenia. These include Neuroreglin 1, DISC1, Dysbindin, G72. (Labrie and Roder, 2010; Powell et al., 2012; Snyder & Gao, 2013). About 50% of identical twins, where at one twin has been diagnosed with schizophrenia, are discordant for schizophrenia. Thus, environmental factors (including environmental stressors and environmental driven molecular alterations to the DNA) undoubtedly interact with genetics in the emergence of psychosis (Mittal, Ellman, & Cannon, 2008). From post-mortem studies there is evidence for molecular alteration (increased methylation of DNA segments so proteins cannot get produced) in NMDA genes and differences in the enzymes which might effect the methylation changes in postmortem tissue (Synder & Gao, 2013). The environmental factors inducing these changes have yet to be identified.

***Pre and peri-natal factors***. Infection of the mother with rubella or influenza virus during the first two trimesters of pregnancy increases the risk of offspring schizophrenia five-fold (Sullivan, 2005) and has been estimated to account for 30% of cases of schizophrenia (Volk & Lewis, 2013). Viral infection confers a greater risk for schizophrenia in those with a positive family history (Mittal, et al., 2008). During the first two trimesters of fetal development, the

GABA-interneurons are migrating to their destination and then differentiating into functional circuits. Inflammatory cytokines from the mother can disrupt this process (Volk & Lewis, 2013). Animal models exposing pregnant dams to infection finds reduction in PV+ interneurons as well as changes in oscillation patterns in the offspring (Powell, et al., 2012).

Obstetric complications, particularly hypoxia, increase the risk of schizophrenia. Hypoxia during delivery raises the risk of schizophrenia to 6% as opposed to the population rate of 1% (Buka, Tsuang, & Lipsitt, 1993). The emergence of psychosis is most pronounced in those suffering obstetric complications who later exhibit developmental delays (Clarke et al., 2011). Moreover, there is support for gene environment interaction, such that the increased risk for obstetric complications is higher in those who have relatives with schizophrenia (Mittal et al., 2008). This type of risk is associated with alterations involving NMDA receptors (Mittal et al., 2008).

Vitamin D deficiency during pregnancy is known to increase the risk for schizophrenia in the offspring. When pregnant mice are restricted on vitamin D in the diet, offspring show alternations in their NMDA receptor function (McGrath, Burne, Feron, Mackay-Sim, & Eyles, 2010).

***Ongoing threats to the integrity of the NMDA receptors***. Mitochondria are "little organs" in cells where energy from food is turned into a form of energy that the cell can use. Mitochondrial dysfunction increases free radical production (molecules with an unpaired electron which damage other molecules) (Verge et al., 2011). Mitochondria protein alterations are found in the brains of those with schizophrenia (Karry, Klein, & Ben Shachar, 2004; Marchbanks et al., 2003). Consistent with alterations in mitochondrial function, levels of free radicals are elevated in the blood of unmedicated persons with schizophrenics and correlate with

psychotic symptoms (Behrens & Sejnowski, 2009). With regard to the interneurons, free radicals can disrupt the enzyme for producing GABA and eventually can produce a loss of the GABA producing interneuron (Cabungcal, Steullet, Kraftsik, Cuenod, & Do, 2013). Moreover, the NMDA receptor will not operate well under conditions of increased free radicals (Do, Cabungcal, Frank, Steullet, & Cuenod, 2009).

Free radicals are "mopped up" by antioxidants such as glutathione and uric acid. Drug-naïve persons with schizophrenia have lower levels of glutathione in plasma and in cerebrospinal fluid (Do et al., 2009). Research suggests that glutathione is particularly relevant for interneurons. Decrements in glutathione are associated with a decrement in PV expression (Cabungcal et al., 2013) and are associated with decrements in gamma oscillations and cognitive performance (Ballesteros et al., 2013). Animal work finds that the reduction in PV+ in fast spiking interneurons is particular to the ventral hypothalamus (Steullet, et al., 2010), the region of the brain which is most critically involved in regulating dopamine release (Grace, 2012). Specifically for creating of psychosis, animal work further finds that a glutathione deficit results in enhanced dopamine release in the N. Accumbens in response to amphetamine (Behrens & Sejnowski, 2010). Glutathione is not only important for mopping up free radicals which can impair the function of the GABAnergic interneurons but glutathione will also increase the signaling at the NMDA receptor (Ladre & Roder, 2010). Allelic variations (that is, genetic variation) in proteins involved in synthesizing glutathione are risk factors for schizophrenia (Behrens & Sejnowski, 2010; Gysin et al., 2007; Powell et al., 2013).

Free radicals can trigger inflammation (Cabungcal et al., 2013). Those with schizophrenia exhibit elevations of S100B in cerebrospinal fluid, a marker of inflammation (Meyer, Schwarz, & Muller, 2011), and according to a meta-analysis have elevations in

inflammatory hormones (Potvin et al., 2008). A downstream event in brain inflammation is the induction of the enzyme Indolamine 2,3 dioxygenase (IDO). IDO leads to enhanced levels of kynurenic acid. Kynurenic acid will block the glycine binding site on the NMDAR receptor (Erhardt, Olsson, & Engberg, 2009). Elevations in kynurenic acid have been found in post-mortem brains and CSF of persons diagnosed with schizophrenia (Labrie & Roder, 2010). Adjunctive treatment with anti-inflammatory drugs (aspirin, COX-2 inhibitors, and minocycline) has proved efficacious in reducing negative symptoms and cognitive deficits in the early onset of schizophrenia (Meyer et al., 2011).

### *Additional Findings Explained by the GABAnergic Interneuron Story*

It has long been a mystery as to why overt psychosis does not emerge prior to adolescence. Puberty is a period during which PV+ interneurons are most susceptible to free radical damage (Cabungcal et al., 2013). In animals which were genetically engineered to have problems generating glutathione, damage to fast spiking interneurons in the ventral hippocampus did not become evident until adolescence (Steullet, et al., 2010).

Marijuana is a risk factor for precipitating schizophrenia in young people. There are receptors for marijuana (cannabinoid 1 receptors) on GABA producing interneurons in the dorsolateral PreFrontal Cortex. Cannabinoids will inhibit GABA release (Eggan, Stoyak, Verrico, & Lewis, 2010). Thus, marijuana increases risk through its impact on the interneurons.

## Hitting the Proper Target

Antipsychotic pharmacological agents include the old neuroleptics (thiothixene, haloperidol) and the newer atypicals (aripiprazole, risperidone, ziprasidone). These agents target D2 receptors; they do not change function of the GABA interneurons. Howes and Kaput speculate (2009, p. 556) “current antipsychotic drugs are not treating the primary abnormality

and are acting downstream". According to Wunderink et al. (2013, e7), "the dopamine system might play a more peripheral role in psychosis than previously thought, while hypothesized primary derangements, such as N-methyl-D-aspartate receptor and/or interneuron dysfunction, remain untouched by dopamine blockade."

**Alternative Treatments for Schizophrenia**

Strategies for targeting the GABA interneurons have been identified. For the most part, these interventions have far fewer negative side effects than the anti-dopamine agents. Tests of these chemicals for decreasing the symptoms of schizophrenia have been positive. There are theoretical reasons for why omega-3s (the fat in fish oil) will target GABA interneuron function. Omega-3s are anti-inflammatory (Arita, 2005). Thus, they should decrease free radical production and protect GABA inter-neurons. Omega-3s also increase brain levels of glutathione (Berger et al., 2008). (Recall, there is a binding site for glutathione in the NMDA receptor, Labrie & Roder, 2010.) A small "N" study by Peet, Brind, Ramchand, Shah, and Vankar (2001) used omega-3s (EPA, a type of omega-3) as a sole treatment for early episode psychosis. If psychosis failed to remit researchers would then treat with antipsychotics. All 12 of those on placebo required anti-dopaminergic meds to control symptoms, while 6/14 did not require meds in the omega-3 group. In children identified as being at high risk for the emergence of psychosis, many treatments including psychotherapy, antipsychotics, and omega-3 were tested for their efficacy in decreasing the emergence of frank psychosis. Cocharane Collaboration (Marshall & Rathbone, 2011) concluded there is no benefit for psychotherapy, family interventions, antipsychotic drugs. The only successful intervention was omega-3s. Over a 52 week period, psychosis emerged in 27.5% of the control group, but in only 4.9% of the omega-3 group (Amminger et al., 2010). Although findings are inconsistent (Fusar-Poli &

Berger, 2012), some tests of omega-3s as added on to antipsychotics have also improved treatment outcomes on both positive and negative symptoms of schizophrenia (Berger et al., 2007; Berger, et al., 2008). With regard to the inconsistent findings, the late David Horribin (2003) cautioned that for those who have been treated with antipsychotics for decades, the omega-3s may not be of much use.

Several other pharmacological interventions targeting the fast spiking, GABA interneurons are available. In the body, N-acetylcysteine is converted to glutathione, an agonist at the NMDA receptor. Sarcosine will increase levels of glycine, another agonist at the NMDA receptor. Although neither N-acetylcysteine nor sarcosine has been evaluated as monotherapies, adjunctive treatments with both compounds have been successful (Berk, 2008;. Tsai & Lin, 2010). Additionally, N-acetylcysteine was able to improve cognitive function and increase GABA oscillations (Lavoie et al., 2008; Carmeli, Knyazeva, Cuenod, & Do, 2012).

It should be noted that targeting the fast spiking GABA neurons requires attention to decreasing systemic inflammation. This implies that changing the total diet is important. Indeed, Peet (2004) emphasizes that to achieve efficacy for Omega-3s, the entire diet may require change. Omega-3s may achieve efficacy by reducing inflammatory factors. It is known that high levels of dietary saturated fats are inflammatory as is high fructose corn syrup (Cani et al., 2008; Ferder, Ferder, & Inserra, 2010). Indeed, high intake of dietary saturated fats is associated with poorer outcome in schizophrenia (Christensen & Christensen, 1988).

**Psychosocial treatments alternatives.** Chemical interventions targeting fast-spiking GABA interneurons are available. While psychosocial treatments do not specifically target fast-spiking GABA interneurons, psychosocial treatment alternatives to drugs have been evaluated. Thus, alternatives are available. Unfortunately, the research on psychosocial

treatment is limited and has been tested primarily for those with first episodes. The extent to which treatments will be efficacious across demographic groups has not been examined. While an in-depth review is beyond the scope of this article, a brief enumeration is provided so that social workers will know that alternatives exist.

Soteria project programs have been tested, in some cases with random assignment, in the US and in Switzerland (Bola & Mosher, 2003). The program is community based with clients residing in a small-home like environment. The expectation of improvement is conveyed. The psychotic symptoms are reframed or described in non-alarming terms. Participation in tasks of daily living is expected.

Mary Olson , a social worker trained in family therapy is currently evaluating Open Dialog in Massachusetts, which has previously been found to be efficacious in Finland (Seikkula, Alakare, & Aaltonen, 2011; Seikkula & Olson, 2003). Open Dialog is similar to Soteria in that psychosis is reframed in non-alarmist terms. Focus is on helping family members communicate with the family member with schizophrenia. A multi-disciplinary team meets with the family several times per week to assist in harmonizing daily functions. Similar to Open-Dialog is the Swedish Parachute Project that reframes the meaning of the psychosis and focus on communication among family members. Bola et al.(2009) characterize the common elements in these programs as “respect for individual patients, a low-stress environment with clear expectations and dependable interpersonal relations, and an effort to involve the patients as active participants in their recovery process “(p. 12). With regard to comparing the psychosocial interventions to medications, Bola et al. (2009) find that outcomes were moderately superior to medications. In addition to family approaches, there is evidence of efficacy for Cognitively Oriented Psychotherapy (Francey et. al., 2010).

## Reflections on the Future

As the developments in the understanding of the neurological mechanisms of schizophrenia have accelerated, change has also impacted the world of clinical treatment. "Psych rehab" has emerged as a model for working with the seriously mentally ill. Rather than being trained to work in Community Mental Health Center offices or state hospitals, psych rehab professionals focus on providing services in the community. Casemanagement services are a primary vehicle for service rather than traditional psychotherapy. Emphasis is on hiring consumers as patient advocates and as casemanagers. The mantras are "empowerment", "consumer choice", and "recovery" (Corrigan, Mueser, Bond, Drake, & Solomon, 2008).

Social workers are involved in providing services in the community and have long been involved in a psycho-educational role (Bentley, Walsh, & Farmer, 2005). The information on anti-dopamine drugs decreasing cortex volume as well as impairing functioning is likely to be widely disseminated. It remains an ethical question whether social workers should be encouraging medication compliance with anti-dopaminergic drugs. If social workers impart information, questions remain about how the negative aspects of medications should be imparted. In the service of obtaining informed consent, social workers can provide information about the existence of pilot programs such as the Open-Dialog treatment and Sorteria. They can also refer to website such as www.Madinamerica.org where psychiatrist, Sandra Steingard, who has also published in the *Washington Post* (2013), has detailed her experience with tapering clients off anti-psychotic medications. Also on the Madinamerica website, accounts from those who have tapered off medications are reported. Social workers can share information with clients and colleagues.

Unfortunately, access to pilot programs or psychiatrists like Sandra Steingard M.D. will be beyond the reach of many clients. It is unlikely that individual physicians will be willing to deviate in their prescribing from usual practice. They must find justification in the research literature for new ways of proceeding. Presently, the newer antipsychotics (ziprasidone, aripiprazole) are big money makers for the drug companies with aripiprazole (Abilify) being the top grossing drug in the U.S. (Lagnado, 2013) and the federal government (Medicaid system) is financing the purchase of the very costly atypicals. Since most clinical research in this country is funded by pharmaceutical companies (Angell, 2010), without a change in the system, research on alternative treatments may not be funded. Peter Gotzsche (2013), a co-founder of the prestigious Cochrane Review, suggests the "big pharma" is relentless in squashing research that might compromise its economic interest, making sure that research regarding alternatives to drugs is not funded and unfavorable results regarding drugs are never published. (Indeed, John Bola has relocated to Hong Kong where it is easier to do innovative work challenging the status quo, J.R. Bola, personal communication, December 15, 2013). It will probably take as big a consumer movement as was witnessed in the early days of the AIDS advocacy to get the government to take action in developing interventions that will help rather than harm. Given the powerful vested interests, it is likely to be a struggle. Hopefully, this paper will inform the social work community so that social workers can advocate for better treatments for their clients.

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