



# Is schizophrenia a metabolic brain disorder? Membrane phospholipid dysregulation and its therapeutic implications

Sahebarao P. Mahadik, PhD<sup>a,b,\*</sup>,  
Denise R. Evans, MD<sup>a,b</sup>

<sup>a</sup>*Department of Psychiatry, Medical College of Georgia, Augusta, GA*

<sup>b</sup>*Medical Research Service, Mental Health Service Line, Veterans Affairs Medical Center,  
1 Freedom Way, Augusta, GA 30904*

## Schizophrenia: a metabolic disorder

Metabolic defects that affect brain structure and function have been contemplated in schizophrenia for more than 100 years. There were two independent lines of investigations: biologic and behavioral. Basic biologic researchers were convinced that each cell type in the body has a unique metabolism that regulates its growth, maintenance, and function, and defective metabolism can result in disease. At the same time, investigators were interested in behavioral disorders; Freud stated that “the difficult birth in itself is merely a symptom of deeper effects that influenced the fetal development,” and Kraepelin stated that “there is something wrong with the brain in schizophrenia” [1]. Now there is substantial evidence for abnormal neurodevelopment and related structural brain abnormalities [2] that may be the result of altered neural cell metabolism.

Cellular metabolic defects result from altered synthesis, usage, and degradation of cellular constituents that maintain normal cellular structure and function; this may be due to genetic defects that can alter the cellular metabolism or a deficiency of dietary essential ingredients, such as essential amino

---

This work was supported in part by Grant No. 5 R01 AT00147 from National Institutes of Health.

\* Corresponding author. Medical Research Service, Mental Health Service Line, Veterans Affairs Medical Center, 1 Freedom Way, Augusta, GA 30904.

*E-mail address:* mahadik@psychnts4.mcg.edu. (S.P. Mahadik).

acids, fatty acids, or vitamins. A large variety of environmental factors, such as stress, drugs of abuse, viral infections, winter climate, and famines, may alter the gene function or dietary availability of essential ingredients or increase breakdown of cellular vital constituents. Before the use of neuroleptics, the role of vitamins for treating metabolic disorders was discovered, and undernutrition or malnutrition was found to affect the brain and behavioral development. At that time, schizophrenia was treated with megadoses of vitamins and proteins. After the discovery of neuroleptics for the treatment of schizophrenia, work was focused on investigating a specific metabolic defect associated with neurotransmitter function. Attempts to correct these neurotransmitter defects by nutritional supplements or by drugs have resulted in marginal therapeutic improvements. They have not had a significant impact on reduction of costs of care or the quality of life of the affected individuals. This situation may be related to the cellular complexity in the brain; its susceptibility to nutritional requirements; environmental influences throughout development; and the contribution of recessive genes, which may increase slightly the risk of developing the disease.

Over the last 50 years, the brain was found to be highly enriched in lipids, and the methodologies for lipid analysis were developed. This work catalyzed the investigations of abnormal lipid metabolism in schizophrenia. Now there is substantial evidence to warrant viewing schizophrenia as a membrane phospholipid metabolic disorder [3–6]. The mechanisms by which a phospholipid metabolic defect may contribute to observed structural brain abnormalities and associated psychopathologies in schizophrenia are mostly speculative, however. The phospholipid metabolic defect involves its altered synthesis and increased breakdown. Neuronal membrane phospholipids are unique in their quality and quantity. These are regulated primarily by their vital constituents, essential polyunsaturated fatty acids (EPUFAs) (ie, fatty acids that are not made in the body and must be consumed in the diet). The contents of membrane phospholipid EPUFAs depend on their dietary availability, enzymatic incorporation into phospholipids, and degradation by specific enzymes or free radicals generated in the body. Brain phospholipid metabolism is predominantly susceptible to a variety of environmental stresses that have been associated with the increased occurrence and severity of schizophrenia. Antipsychotics used for the treatment of schizophrenia have been found to affect EPUFA metabolism and membrane phospholipids in the brain. The metabolism of EPUFAs is crucial in brain and behavioral development through their role in membrane structure and function, primarily in signal transduction of several neurotransmitters and growth. Finally, membrane EPUFA abnormalities are corrected through proper dietary supplementation. Because antipsychotic medication is the current standard of care in the treatment of schizophrenia, use of EPUFAs for the augmentation of antipsychotic therapeutic effects may be the preferred strategy.

## **Dysregulation of plasma membrane phospholipid metabolism in schizophrenia**

The plasma membrane performs several vital functions, such as transport of nutritional ingredients in and bioactive molecules out, signal transduction mediated by membrane receptors, and cell-cell interactions. These functions are regulated by the cell-specific composition of proteins and lipids. Evidence indicates that these membrane functions are altered in schizophrenia, primarily as a result of changes in the quality and quantity of phospholipids [4,6]. Most of this evidence is based on studies in peripheral cell membranes. The mechanisms of phospholipid metabolism are conserved throughout the body, however. Defects are considered to be similar in the brain membranes, whereas the pathophysiologic consequences may differ in quality and quantity. Most of the evidence indicates that membrane pathology in schizophrenia is primarily related to altered phospholipid metabolism. Brain membranes have a unique composition of phospholipids, which may explain the preferential consequence on brain structure and function in schizophrenia.

### *Membrane phospholipid metabolism in schizophrenia*

Altered contents of membrane phospholipids and bound fatty acids, which are indices of dysregulation of membrane phospholipid metabolism, have been reported in schizophrenia since the 1960s. As the unique chemical nature of brain membrane phospholipids and their crucial role in brain growth and neurotransmitter receptor-mediated signal transduction are becoming clearer, interest is growing in defining the phospholipid metabolic defects and investigating the underlying mechanisms. The dysregulation of phospholipid metabolism in schizophrenia seems to involve their decreased synthesis and increased breakdown. It is hoped that such information will lead to effective therapeutic strategies.

### *Brain membrane phospholipids and their fatty acids and functional organization*

Brain membranes constitute greater than 66% phospholipids by mass versus 33% in peripheral tissues [7,8]. These phospholipids are composed primarily (>90%) of four types, which differ in chemical group attached at the R3 position: choline, ethanolamine, serine, and inositol in decreasing amounts (Fig. 1). Each type exists in a large number of molecular species that differ in type of fatty acids attached at positions R1 and R2. The R1 position is always occupied by nonessential fatty acids (Fig. 2) that are made in the body or are amply available in the diet from animal fat. The R2 position is occupied exclusively by EPUFAs, however, primarily in equal quantities of arachidonic acid (AA), also known as a key  $\omega$ -6 fatty acid, or docosahexaenoic acid (DHA), also known as a key  $\omega$ -3 fatty acid (Fig. 2). Greater than 90% of the R2 fatty acids are AA and DHA in the brain versus

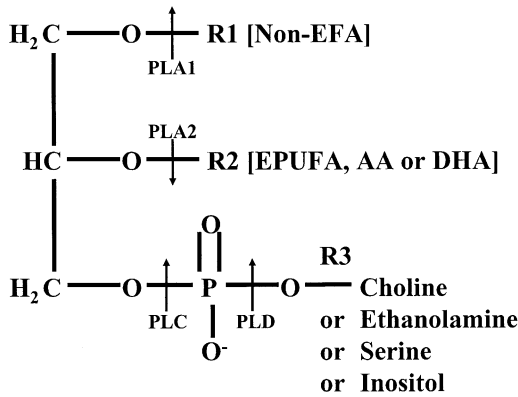


Fig. 1. Molecular formula of a typical membrane phospholipid. R1, R2, and R3 represent the positions on the glycerophosphate backbone, which are generally occupied by nonessential fatty acids (Non-EFAs), essential polyunsaturated fatty acids (EPUFAs), and head groups (choline, ethanolamine, serine, or inositol). Arrows indicate the sites of the phospholipid breakdown by enzymes, phospholipase A1 (PLA1), phospholipase A2 (PLA2), phospholipase C (PLC), and phospholipase D (PLD), which are activated specifically and differentially during membrane signal transduction.

less than 20% in the nonneural tissues. These EPUFAs also are selectively susceptible to breakdown by lipolytic enzymes (genetic) or nonenzymatic processes (environmental, free radicals) under adverse physiologic and environmental situations [9,10]. These EPUFAs also have a high turnover through receptor-mediated signal transduction by several neurotransmitters and growth factors [11–14]. Substantial amounts of AA and DHA or their precursors must be consumed in the diet. These phospholipids and their fatty acids are differentially organized forming a bilayer in plasma membranes of neurons and glia (Fig. 3). The external environment communicates with the intracellular machinery via their interaction with receptors for neurotransmitters and growth factors, cell adhesion molecules, and ion and nutrition transporters embedded in the lipid bilayer, which regulates their activities. Also, these membrane organizations of neuronal soma, neuropile, and nerve endings with respective neurotransmitters differ significantly from each other. The phospholipid defect in schizophrenia may be a primary defect in EPUFA metabolism that may lead to structural and functional abnormalities observed in schizophrenia [15–17].

#### *Membrane phospholipid contents in schizophrenia*

Rotrosen and Wolkin [3] initially presented a membrane phospholipid hypothesis of schizophrenia based on a comprehensive survey of the literature. Those earlier studies in peripheral cells and studies reported since then, which included brain tissues, indicated, however, a large degree of variabil-

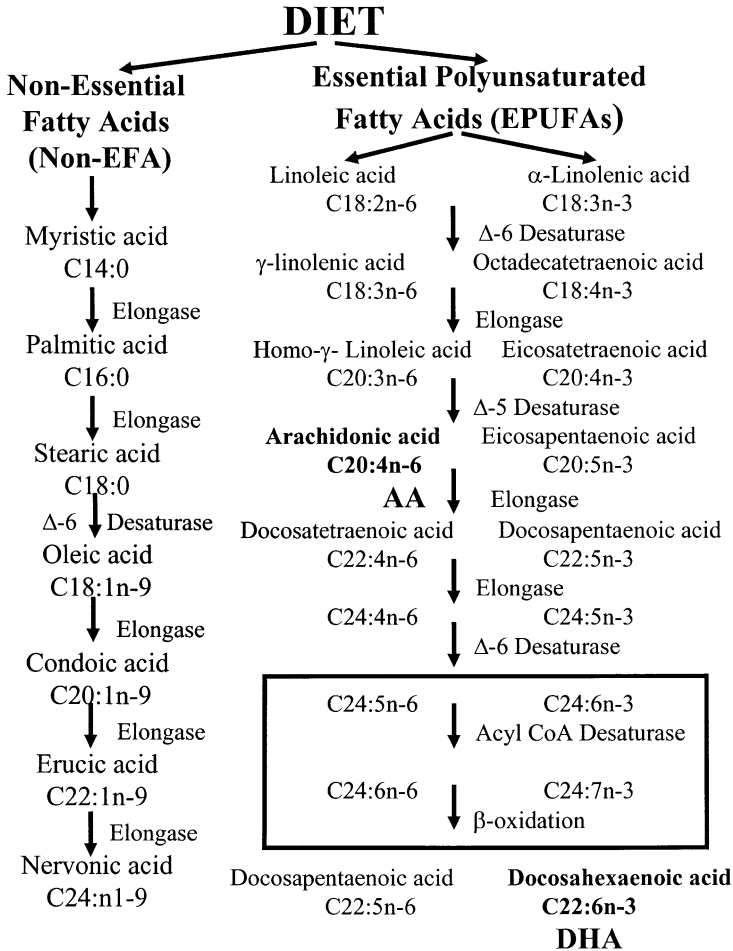


Fig. 2. Source and metabolic pathways of nonessential fatty acids (Non-EFAs) and essential polyunsaturated fatty acids (EPUFAs). Each fatty acid is designated as follows: C, number of carbons; n, number of double bonds; last numbers indicate the type of fatty acid such as n-9, n-7, n-6, and n-3. Bold-lettered fatty acids, arachidonic acid (C20:4n-6, AA) and docosahexaenoic acid (C22:6n-3, DHA), are the key EPUFAs, which are enriched in the brain, and their metabolism is altered selectively in schizophrenia.

ity in the contents of various species of phospholipids [18,19]. Because many of these studies were done in medicated chronic schizophrenia patients, some of the variability was attributed to years of illness and medication effects. Studies in drug-naïve, first-episode psychotic patients reported reliable and reproducible reduction in red blood cells [20] and in skin fibroblasts from drug-naïve, first-episode and chronic medicated patients [21]. Phosphatidylethanolamine is selectively enriched in AA and DHA.

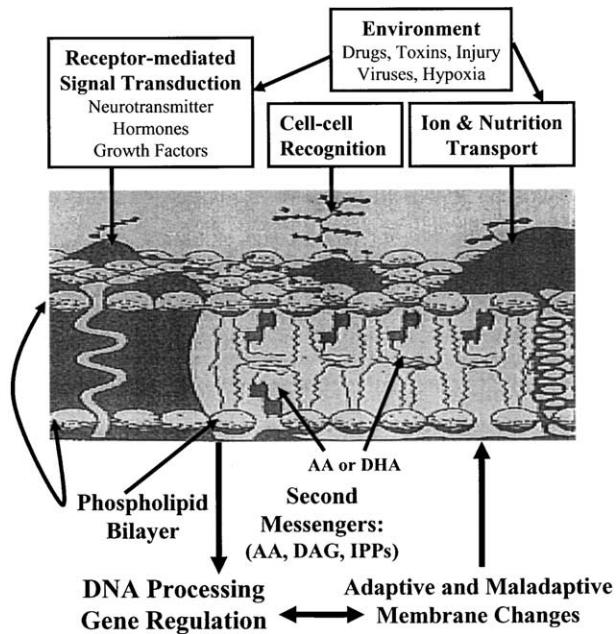


Fig. 3. Plasma membrane model shows the phospholipid organization and its role in the regulation of extracellular environmental effects on the cellular function. AA, arachidonic acid; DHA, docosahexaenoic acid; DAG, diacyl glycerol; IPPs, inositol polyphosphates. Arrows indicate the direction of the functional effects.

### *Membrane essential polyunsaturated fatty acid contents in schizophrenia*

The most consistent reductions of EPUFA in schizophrenia have been reported in the contents of AA and DHA, even at the onset of psychosis [22–26]. The degree of reduction also has been found to correlate with the severity of symptoms and cognitive deficits. These findings have been supported by some epidemiologic data that indicate the increased dietary intake of these EPUFAs, particularly DHA, correlated with reduced decrements in membrane contents of DHA and with improved psychopathology [27–30]. These data led to the investigation of the mechanisms underlying reductions in the contents of AA and DHA.

### *Altered phospholipid synthesis in schizophrenia*

#### *Reduced dietary intake of essential polyunsaturated fatty acids*

As indicated earlier, phospholipid metabolism is regulated primarily by availability of the right species of  $\omega$ -6 and  $\omega$ -3 EPUFAs [16,31]. Plants make both of these primary EPUFAs. Animals do not make these and must obtain them through their diet. These EPUFAs are converted further and stored in large quantities by animals, particularly fish. Burr and Burr [32]

first discovered that fatty acids are essential for brain development. Since then, studies in animals and humans have found that availability of these EPUFAs, particularly DHA, is crucial for brain development and its maintenance throughout life [33–38].

Christinsen and Christinsen [27] initially made the direct association of dietary intake of  $\omega$ -3 EPUFAs and the outcome of schizophrenia worldwide. Since then, several environmental situations, such as famine or the winter season, that may reduce the intake of EPUFAs have been suggested to affect brain development and changes in rates of schizophrenia [29]. Peet and coworkers [28] indicated that dietary intake and membrane levels of  $\omega$ -3 EPUFAs correlate with the outcome; this is potentially important for a therapeutic strategy (see later).

#### *Defective use of precursor essential polyunsaturated fatty acids*

AA and DHA generally are made in the body from their precursor, linoleic acid and  $\alpha$ -linolenic acid, which are consumed in the diet from both animal or plant foods. These precursors are converted to AA and DHA by the same set of enzymes: elongases, desaturases, and fatty acid acyl transferases (see Fig. 2) [31]. There is some evidence that the desaturation and incorporation of DHA into phospholipids may be reduced, owing to defective desaturase or fatty acid acyl transferase in schizophrenia [4,17]. It also has been suggested that increased intake of  $\omega$ -6 EPUFAs may have affected the DHA membrane contents of competition with common enzymes. It will be important for genetic studies to investigate the role of these enzymes in schizophrenia.

#### *Increased phospholipid breakdown in schizophrenia*

Increased phospholipid breakdown (increased contents of phosphodiester) and decreased synthesis (decreased contents of phosphomonoesters) in relevant regions of the brain have been reported using  $^{31}\text{P}$  magnetic resonance spectroscopy in first-episode psychotic and chronic medicated schizophrenic patients [39–45]. These phosphodiester and phosphomonoester changes have been affected by antipsychotics, depending on the type of antipsychotic and duration of treatment, and correlate with the psychopathology. Increased phospholipid breakdown seems to involve at least two mechanisms: phospholipases and free radicals.

#### *Breakdown of phospholipids by phospholipases in schizophrenia*

There is a large list of phospholipases. Phospholipase A2 (PLA2), which hydrolyzes the EPUFAs from R2 position, and phospholipase C (PLC), which hydrolyzes lipids generating second messengers such as inositol polyphosphate and diacyl glycerol, are the most extensively studied (see Fig. 1). These vital phospholipases normally are regulated by cell signal mechanisms. Their levels may increase under noxious stimulus or under

pathophysiologic situations, generally for tissue repair purposes. Viral infections, fevers, and ischemic birth complications also have been known to increase PLA2. This increase in PLA2 can result in reduction of EPUFAs, particularly during crucial stages of brain development. Increased levels of PLA2 in schizophrenia are implicated in reduced membrane EPUFAs. Inconsistent increases in levels of PLA2 and polymorphism in its gene have been reported in schizophrenic patients [10,46,47]. It was suggested that if PLA2 is increased in schizophrenia, it may be related to increased lipid peroxidation for repair purposes [48].

#### *Breakdown of phospholipids by free radicals in schizophrenia*

There is now substantial evidence for increased free radical-mediated breakdown of phospholipids (specifically bound EPUFAs) in schizophrenia even at the onset of psychosis [9,10,49,50]. The association between reduced membrane EPUFAs, an increase in their peroxidation products, and increased psychopathology also has been reported [26,51,52]. The evidence indicates that enzymatic and nonenzymatic antioxidant defense is impaired in schizophrenia. Cellular levels of free radicals may be increased by both of these mechanisms and by the illness itself. Further studies to understand the nature of antioxidant defense in schizophrenia may help to develop therapeutic strategies (see later).

#### *Antipsychotic treatment effects on phospholipid metabolism in schizophrenia*

Antipsychotics have been found to have either pro-oxidant (ie, increased peroxidative breakdown) or antioxidant effects on cellular lipid metabolism, based on differences in their chemical properties [10,53–55]. Haloperidol has been found to be converted to a free radical in the brain, and that free radical is found to cause neuronal damage [56]. Several atypical antipsychotics have been found to increase membrane phospholipid EPUFAs, particularly AA and DHA [26,57,58]. These changes correlated with improved psychopathology. Although the exact mechanisms of their action are still unclear, it has been suggested that atypical antipsychotics might inhibit the phospholipases and increase the antioxidant defense enzymes and do not cause lipid peroxidation similar to haloperidol [59].

Long-term treatment with several atypical antipsychotics but not with haloperidol was found to increase levels of apolipoprotein D (ApoD) in the brain and plasma of rats [60,61]. ApoD is an AA binding protein, which transports AA through blood throughout body and across plasma membranes into the cell. It may function intracellularly in prevention of AA destruction by free radicals and may make AA available for membrane phospholipid synthesis. Because AA metabolism is linked with DHA, increase in AA levels also may result in a DHA increase. Elevated levels of ApoD also have been reported in postmortem brains of schizophrenic patients [62] and in plasma of drug-naïve, first-episode psychotic patients. An even larger increase has been noted in patients treated with atypical

antipsychotics [63]. These studies indicate that this may be one of the novel mechanisms of action of atypical antipsychotics. Increasing membrane phospholipid EPUFAs may be partly responsible for the associated improved symptoms. Clozapine has been found to increase plasma triglycerides, and olanzapine has been found to increase cholesterol. These lipid changes have been found to affect membrane EPUFA metabolism.

*Implications of the dysregulation of membrane phospholipid metabolism to schizophrenia*

As indicated earlier, phospholipids, by their unique contents of EPUFA, play a crucial role in brain and behavioral development [16,37,38]. Altered metabolism in schizophrenia may have implications for neurodevelopmental deficits and behavioral deficits. Behavioral deficits may be related to abnormal development of neuronal circuitry and membrane receptor signal transduction by several neurotransmitters and neurotrophic factors.

*Membrane phospholipid metabolism and abnormal neurodevelopment in schizophrenia*

A deficiency of DHA during the embryonic stage in monkeys has been reported to cause a wide range of morphologic deficits and functional deficits, such as attention deficit, deficit in eye acuity, hyperactivity, and polydipsia [34]. Some of these deficits are similar to structural and behavioral deficits found in schizophrenia. Studies on famine, fevers, and birth complications during early brain development that have reported higher rates of schizophrenia indicate that these events must have direct effects on brain development resulting from EPUFA deficiency. There is no direct evidence yet for such a theory, however. Future studies in high-risk populations for EPUFA deficiency by intervention with EPUFA supplementation during the crucial period of brain development and follow-up through the risk period of onset of development of schizophrenia may help to obtain such evidence. Such studies may be difficult to carry out, but neurodevelopmental deficits can be prevented only during the crucial growth period and cannot be corrected when stable neural circuitry is established.

*Membrane phospholipid metabolism and abnormal signal transduction in schizophrenia*

Brain membrane phospholipids play a vital role in receptor-mediated signal transduction by several neurotransmitters [12–14]. These play a direct role in the generation of second messengers as their metabolites. AA, DHA, diacylglycerol, and inositol polyphosphates are generated as second messengers by dopamine, serotonin, glutamate, acetylcholine, substance P, and  $\gamma$ -aminobutyric acid, all of which are implicated in schizophrenia. In addition, phospholipids are involved in signal transduction by nerve growth factor,

brain-derived neurotrophic factors, and basic fibroblast growth factors that also are implicated in the pathophysiology of schizophrenia. A few studies have shown altered signal transduction based on altered turnover and metabolism of inositol and AA in schizophrenic patients after treatment with antipsychotics [64–66]. Based on such findings and altered phospholipid metabolism, a generalized role for central nervous system signal transduction has been proposed in schizophrenia [67]. Signal transduction mechanisms are crucial for precise information processing, which is found to be altered in schizophrenia [68].

### **Dysregulation of phospholipid metabolism in schizophrenia: therapeutic implications**

Schizophrenia has been treated with a variety of antipsychotics. Analysis of the data has indicated that the average symptom reduction is 17.3% on typical antipsychotics, such as chlorpromazine, haloperidol, and fluphenazine, and 16.6% on newer atypical antipsychotics [69]. These improvements have not made much difference in the employment rate and reintegration into society of patients [70].

Evidence indicates that the dysregulation of phospholipid metabolism may be related primarily to availability or metabolism of EPUFAs in schizophrenia. Studies have shown that disorders associated with EPUFA deficits can be prevented and some of the cellular pathophysiologies can be corrected by proper supplementation of the diet. Supplementation with antioxidants such as vitamins A and C and beta-carotene alone can prevent the loss of membrane EPUFAs and restore part of the EPUFAs. Supplementation with a combination of EPUFAs and antioxidants may be preferred for more effective correction of EPUFA deficits. This information has helped to initiate the adjunctive use of EPUFAs and their metabolites, such as prostaglandins, to improve the outcome of schizophrenia [15,16,71]. These studies also have shown variable therapeutic results, however, including no therapeutic effects in one study [72]. To prevent neurodevelopmental abnormalities, supplementation must be done during the early, even embryonic, period of development.

#### *Supplementation of essential polyunsaturated fatty acids in schizophrenia*

All the EPUFA supplementation studies done so far are in chronic schizophrenia patients treated with a variety of typical and atypical antipsychotics. These studies have indicated several crucial issues that must be considered in designing and carrying out such studies:

1. *Age of the patients and years of illness:* This may be the most important issue because age has been associated with the potential for antioxidant defense [73], and the years of illness and treatment, particularly with

typical antipsychotics, may lead to a state of membrane pathology, which may be difficult to correct. Fenton and colleagues [71], who did not find any therapeutic effect, suggested supplementation in younger patients in the early stages of illness.

2. *Adjunctive medication:* Typical antipsychotics, such as haloperidol, have pro-oxidant properties [55]. These medications also can affect EPUFA metabolism [4]. Newer atypical antipsychotics have antioxidant effects and have been found to improve membrane EPUFA levels [26,52,56].
3. *Type of EPUFA:* Although earlier studies reported efficacy of  $\omega$ -6 fatty acids [74], more recently a few well-designed studies reported that  $\omega$ -3 eicosapentaenoic acid (EPA) alone may be adequate to correct the membrane EPUFA deficits and improve the psychopathology [74,75]. The use of a mixture of EPA and DHA still may be preferred, however, because a large percentage of EPA is converted to prostaglandins and may not be adequate as a substrate for DHA, which is a major neuronal membrane EPUFA.
4. *Dose and the quality of  $\omega$ -3 EPUFA:* It is known that high doses of EPUFAs, if not balanced with dietary antioxidants, may increase the levels of peroxides that are known to be toxic to several plasma membrane functions, including neurotransmitter signal transduction [76,77].
5. *Duration of treatment:* Earlier studies suggested that supplementation for at least 4 months is required to restore red blood cells and brain membrane EPUFAs to steady-state levels [16]. One study indicated, however, that supplementation with EPA had therapeutic effects within a few weeks, indicating a possible indirect role for EPA or for its metabolites [75].
6. *Placebo control:* Because all psychiatric disorders show a significant placebo effect on symptom reduction, well-designed placebo-controlled, dose-ranging studies would be crucial to determine the therapeutic effects [58].

Specific findings from some of the more recent studies are described here. A dose-ranging study with ethyl-EPA (placebo or 1, 2, or 4 g/d for 12 weeks) in patients with persistent schizophrenic symptoms on clozapine or atypical antipsychotics (olanzapine, risperidone, or quetiapine) or one of the typical antipsychotics has been published [58]. Placebo was 4 g/d of liquid paraffin, which has been used up to 15 to 30 g/d as a laxative. No serious adverse effects were reported. It was concluded that 2 g/d had the maximum therapeutic effect. Patients on typical antipsychotics and new atypical drugs did not show improvement over patients on placebo, however, who showed significant improvements from baseline. The clozapine group had little placebo effect, and responses to 2-g dose of ethyl-EPA were substantially better than placebo. The elevated levels of membrane EPA or DHA did not correlate with clinical improvements, but levels of AA did show strong correlation. Authors explained this as an inhibition of AA incorporation by ethyl-EPA

in membranes. Ethyl-EPA is a potent inhibitor of PLA<sub>2</sub>, however, that may upset some of the effects on AA. Because these studies found a therapeutic effect of 2 g of ethyl-EPA in a small group of patients, further work is needed to explore the full therapeutic potential of EPUFAs.

Because all the published studies that have reported therapeutic effects of EPUFA supplementation in schizophrenia have been done by only one group of investigators, it is important to have replication studies done by other investigators. It may be preferable to do multinational studies, in which patients differ significantly in racial background, lifestyle, socioeconomic status, and dietary patterns, because all of these factors have a significant influence on membrane phospholipid EPUFA metabolism. Peet and Horrobin [58] found that the dietary variability among patients also had a significant effect on the therapeutic effects of EPA supplementation.

#### *Supplementation of a combination of essential polyunsaturated fatty acids and antioxidants in schizophrenia*

The use of a combination of EPUFAs and antioxidants (eg, vitamins E and C) for supplementation may be preferable [78] because the evidence is increasing for increased oxidative stress and oxidative cellular injury in schizophrenia [9,10,49]. Antioxidants have been found to be effective in protecting membrane EPUFAs, in addition to preventing oxidative damage of vital cellular proteins, mitochondria, and DNA. Many studies have reported variable therapeutic effects of dietary antioxidants, primarily vitamin E on tardive dyskinesia and cognitive deficits in chronic medicated schizophrenic patients [10,49,51,79–81]. Supplementation with vitamin C, an effective intracellular antioxidant, has not been tried yet, although its use in preventing intracellular peroxidative injury and restoring active vitamin E for prevention of membrane lipid peroxidation has been suggested by many studies [78,81].

The authors have done one study with 4-month supplementation of a combination of EPA: DHA (360:240) and vitamins E and C (800 IU:1 g) per day in two equal doses in 34 chronic schizophrenic patients on stable typical and atypical medications [52]. All patients showed greater than 25% reductions in most of the psychopathologic scores, and these effects were sustained significantly 4 months after termination of supplementation. The study did not have a placebo group. The membrane EPA and DHA levels were elevated from baseline, however, to equal or even slightly higher than matched normal controls without any change in the plasma lipid peroxides; this indicated that the low-dose EPUFA treatment is adequate to correct the preexisting membrane EPUFA deficits, and probably antioxidants prevented the degradation. Pretreatment AA levels were similar to normal controls, which were significantly reduced at posttreatment and returned to pretreatment levels after 4 months of termination of supplementation. Supplementation of  $\omega$ -3 EPUFAs such as EPA alone [58] or a mixture of EPA

and DHA, as in the authors' study, probably reduces AA incorporation in membranes by competition. It is also possible that it may be necessary to increase the antioxidants in supplementation because AA is selectively vulnerable to peroxidation under oxidative stress that exists in schizophrenics.

Further placebo-controlled supplementation studies with a combination of EPUFAs (EPA plus DHA) and a mixture of vitamins E and C should be considered. Although EPA is effective in reducing some symptoms, it is not a major membrane fatty acid. Levels of its metabolites such as eicosanoids may increase at high doses. These metabolites have not been found to be therapeutic and may have some unwanted effects. Also, the reduction of membrane AA either by competition for incorporation or by inhibition of PLA2 is not good. Normal levels of membrane AA and PLA2 are crucial for membrane receptor-mediated signal transduction of several neurotransmitters and growth factors in schizophrenia.

#### *Augmentation of antipsychotic treatment effects by essential polyunsaturated fatty acid supplementation in schizophrenia*

As indicated earlier, EPUFA supplementation in schizophrenia is being studied as an adjunct to conventional treatments with antipsychotics. A study by Peet and coworkers [58] found that therapeutic effects of EPA supplementation in clozapine-treated patients differed from effects in patients with typical antipsychotics and other newer atypical antipsychotics. This finding creates an important dilemma for these types of studies. Typical antipsychotics, such as haloperidol, fluphenazine, and chlorpromazine, as was indicated earlier, have been found in animals to induce oxidative stress and oxidative injury, primarily through increased EPUFA peroxidation. They also interfere with EPUFA incorporation in membranes [9,10]. To limit this confound, it may be necessary to use antioxidants in combination with EPUFAs as discussed earlier. Clozapine and some newer atypical antipsychotics have been found to increase membrane EPUFA levels by themselves [26,57,58]. One mechanism proposed is that atypical antipsychotics induce apolipoprotein D (AA binding protein), which may protect AA from possible peroxidation in schizophrenia. Atypical antipsychotics such as olanzapine and risperidone have been found to have neuroprotective effects on central nervous system cholinergic activity with improved cognitive performance in rats [82]. It is also important to determine the effects of EPUFAs on the pharmacodynamics of these antipsychotics.

#### **Summary**

The dysregulation of membrane phospholipid metabolism exists throughout the body from the onset of psychosis in schizophrenic patients. This dysregulation is primarily due to altered contents of phospholipid bound EPUFAs, AA and DHA. These EPUFAs are highly enriched in the brain

and are crucial for brain and behavioral development. A phospholipid metabolic defect may preexist the onset of psychosis, even through early embryonic stages. Because these membrane phospholipids play a crucial role in the membrane receptor-mediated signal transduction of several neurotransmitters and growth factors, their altered metabolism may contribute to the reported abnormal information processing in schizophrenia. Severity of symptoms seems to correlate with the membrane AA and DHA status, which is influenced by patients' dietary intake and lifestyle. Such a metabolic defect can be prevented, however, and some membrane pathology can be corrected by dietary supplementation with a combination of AA and DHA and antioxidants such as vitamins E and C. In schizophrenia, it may be advisable to provide supplementation at the early stages of illness, when brain has a high degree of plasticity. Finally, at this time, supplementation has to be considered as an augmentation of conventional antipsychotic treatment.

## References

- [1] Kraepelin E. *Dementia praecox and paraphrenia*. Edinburgh: Livingstone; 1919.
- [2] Waddington JL, Buckley PF (eds). *The neurodevelopmental basis of schizophrenia*. Austin, TX: RG Landes Company, Chapman & Hall; 1996.
- [3] Rotrosen J, Wolkin A. Phospholipid and prostaglandin hypotheses of schizophrenia. In: Meltzer HY (ed). *Psychopharmacology: the third generation of progress*. New York: Raven Press; 1987. p. 759–764.
- [4] Horrobin DF, Glen AIM, Vaddadi KS. The membrane hypothesis of schizophrenia. *Schizophr Res* 1994;13:195–207.
- [5] Horrobin DF. Schizophrenia as a membrane lipid disorder, which is expressed throughout the body. *Prostaglandin Leukotr Essent Fatty Acids* 1996;55:3–7.
- [6] Horrobin DF. The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. *Schizophr Res* 1998;30:193–208.
- [7] Suzuki K. Chemistry and metabolism of brain lipids. In: Seigel DJ, Albers RW, Agranoff BW, et al (eds). *Basic neurochemistry*. 3rd ed. Boston: Little, Brown; 1981. p. 355–70.
- [8] Horrocks LA, Kanfer JN, Porcellati G (eds). *Phospholipids in the nervous system*. Vol 2. New York: Raven Press; 1982.
- [9] Mahadik SP, Mukherjee S. Free radical pathology and antioxidant defense in schizophrenia: a review. *Schizophr Res* 1996;19:1–17.
- [10] Mahadik SP, Sitasawad S, Mulchandani M. Membrane peroxidation and the neuropathology of schizophrenia. In: Peet M, Glen I, Horrobin DF (eds). *Phospholipid spectrum disorders in psychiatry*. Lancashire: Marius Press; 1999. p. 99–111.
- [11] Agranoff B. Lipids. In: Siegel GJ, Albers RW, Agranoff BW, Katzman R (eds). *Basic neurochemistry*. 4th ed. Boston: Little, Brown; 1989. p. 91–107.
- [12] Axelrod J. Receptor-mediated activation of phospholipase A<sub>2</sub> and arachidonic acid release in signal transduction. *Biochem Soc Trans* 1990;18:503–7.
- [13] Piomelli D, Pilon C, Giros B, et al. Dopamine activation of the arachidonic acid cascade as a basis for D1/D2 receptor synergism. *Nature* 1991;353:164–7.
- [14] Farooqui AA, Hirashima Y, Horrocks LA. Brain PLAs and their role in signal transduction. In: Toffano G, Murphy MG, Bazan N, editors. *Neurobiology of essential fatty acids*. New York: Plenum Press; 1992. p. 11–25.
- [15] Peet M, Glen I, Horrobin D (eds). *Phospholipid spectrum disorders in psychiatry*. Lancashire: Marius Press; 1999.

- [16] Mahadik SP, Evans D. Essential fatty acids in the treatment of schizophrenia. *Drugs Today* 1997;33:5–17.
- [17] Mahadik SP, Shendarkar NS, Scheffer R, et al. Utilization of precursor essential fatty acids in culture by skin fibroblasts from schizophrenic patients and normal controls. *Prostagland Leukotr Essent Fatty Acids* 1996;55:65–70.
- [18] Horrobin DF, Manku MS, Hillman H, et al. Fatty acid levels in the brains of schizophrenics and normal controls. *Biol Psychiatry* 1991;30:795–805.
- [19] Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. *Schizophr Res* 2000;42:7–17.
- [20] Keshavan MS, Mallinger AG, Pettegrew JW, et al. Erythrocyte membrane phospholipids in psychotic patients. *Psychiatry Res* 1993;49:89–95.
- [21] Mahadik SP, Mukherjee S, Correnti EE, et al. Plasma membrane phospholipid and cholesterol distribution of skin fibroblasts from drug-naive patients at the onset of psychosis. *Schizophr Res* 1994;13:239–47.
- [22] Yao JK, van Kammen DP, Welker JA. Red blood cell membrane dynamics: II. fatty acid composition. *Schizophr Res* 1994;13:217–26.
- [23] Glen AIM, Glen EMT, Horrobin DF, et al. A red cell membrane abnormality in a subgroup of schizophrenic patients: evidence for two diseases. *Schizophr Res* 1994;12:53–61.
- [24] Mahadik SP, Mukherjee S, Correnti EE, et al. Plasma membrane phospholipid fatty acid composition of cultured skin fibroblasts from schizophrenic patients: comparison with bipolar and normal subjects. *Psychiatry Res* 1996;63:133–42.
- [25] Assies J, Lieverse R, Vreken P, et al. Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. *Biol Psychiatry* 2001;49:510–22.
- [26] Khan MM, Evans DR, Gunna V, et al. Reduced erythrocyte membrane essential fatty acids and increased lipid peroxides in schizophrenia at the never-medicated first-episode of psychosis and after years of treatment with antipsychotics. *Schizophr Res* 2002;58:1–10.
- [27] Christinsen O, Christinsen E. Fat consumption and schizophrenia. *Acta Psychiatr. Scand* 1988;78:587–91.
- [28] Peet M, Laugharne J, Rangarajan N, et al. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. *J Psychiatr Res* 1995;29:227–32.
- [29] Mahadik SP, Mulchandani M, Hegde MV, et al. Cultural and socio-economic differences in dietary intake of essential fatty acids and antioxidants: effects on the course and outcome of schizophrenia. In: Peet M, Glen I, Horrobin D (eds). *Phospholipid spectrum disorders in psychiatry*. Lancashire: Marius Press; 1999. p. 167–79.
- [30] Arvindakshan M. Essential polyunsaturated fatty acid metabolism in schizophrenia outcome. PhD Thesis, Pune University, Pune, India, 2002.
- [31] Thompson GA (ed). *The regulation of membrane lipid metabolism*. 2nd ed. Boca Raton, FL: CRC Raven Press; 1992.
- [32] Burr GO, Burr MM. On the nature and the role of the fatty acids essential in nutrition. *J Biol Chem* 1930;85:587–621.
- [33] Carlson SE, Carver JD, House SC. High fat diets varying ratios of polyunsaturated to saturated fatty acids and linolenic acid, a comparison of rat neural and red cell membrane phospholipids. *J Nutr* 1986;116:718–25.
- [34] Neuringer M, Conner WE, Lin DS, et al. Biochemical and functional effects of prenatal and post-natal  $\omega$ -3 fatty acid deficiency on retina and brain in rhesus monkeys. *Proc Natl Acad Sci U S A* 1986;83:4021–5.
- [35] Anderson GJ, Connor WE, Corliss JD. Docosahexaenoic acid is the preferred dietary n-3 fatty acid for the development of the brain and retina. *Pediatr Res* 1990;27:89–97.
- [36] Bourre JM, Bonneil M, Chaudiere J, et al. Structural and functional importance of dietary polyunsaturated fatty acids in the nervous system. In: Toffano G, Murphy MG, Bazan NG (eds). *Neurobiology of essential fatty acids*. New York: Plenum Press; 1992. p. 211–29.

- [37] Simopoulos AP. Omega-3 fatty acids in health and disease, and growth and development. *Am J Clin Nutr* 1991;54:438–63.
- [38] Wainwright PE. Do essential fatty acids play a role in brain and behavioral development? *Neurosci Biobehav Res* 1992;16:193–205.
- [39] Pettegrew JW, Keshavan MS, Panchalingam K, et al. Alterations in brain high energy phosphate and membrane phospholipid metabolism in first-episode, drug-naive schizophrenics: a pilot study of dorsal prefrontal cortex by in vivo  $^{31}\text{P}$  NMRS. *Arch Gen Psychiatry* 1991;48:563–8.
- [40] Fujimoto T, Nakano T, Takano T, et al. Study of chronic schizophrenics using  $^{31}\text{P}$  magnetic resonance chemical shift imaging. *Acta Psychiatr Scand* 1992;86:455–62.
- [41] Keshavan MS, Sanders RD, Pettegrew JW, et al. Frontal lobe metabolism and cerebral morphology in schizophrenics:  $^{31}\text{P}$  MRS and MRI studies. *Schizophr Res* 1993;10:241–6.
- [42] Stanley JA, Williamson PC, Drost DJ, et al. Membrane phospholipid metabolism and schizophrenia: an in vivo  $^{31}\text{P}$ -MR spectroscopy study. *Schizophr Res* 1994;13:209–15.
- [43] Fukuzako H, Fukuzako T, Takeuchi K, et al. Phosphorus magnetic resonance spectroscopy in schizophrenia: correlation between membrane PL metabolism in the temporal lobe and positive symptoms. *Progr Neuropsychopharmacol Biol Psychiatry* 1996;20:629–40.
- [44] Fukuzako H, Fukuzako T, Kodama S, et al. Haloperidol improves membrane phospholipid abnormalities in temporal lobes of schizophrenic patients. *Neuropsychopharmacology* 1999;21:542–9.
- [45] Jensen JE, Al-Salmaan YM, Williamson PC, et al. Region-specific changes in phospholipids metabolism in chronic, medicated schizophrenia. *Br J Psychiatry* 2002;180:39–44.
- [46] Katila H, Appleberg B, Rimon R. No differences in phospholipase-A2 activity between acute psychiatric patients and controls. *Schizophr Res* 1997;26:103–5.
- [47] Choudhari KV, Brandstaetter B, Semwal P, et al. Association studies of cytosolic phospholipase A2 polymorphisms and schizophrenia among two independent family-based samples. *Psychiatric Gen* 2001;11:207–12.
- [48] Scheffer RE, Bradley J, Mahadik SP. Elevated lipid peroxidation and phospholipase A2: possible mechanism of the lower cell membrane essential polyunsaturated fatty acids in schizophrenia. *Biol Psychiatry* 1999;43:101.
- [49] Reddy R, Yao J. Free radical pathology in schizophrenia: a review. *Prostaglandin Leukot Essent Fatty Acids* 1996;55:33–43.
- [50] Mahadik SP, Mukherjee S, Scheffer R, et al. Elevated plasma lipid peroxides at the onset of nonaffective psychosis. *Biol Psychiatry* 1998;43:674–9.
- [51] Peet M, Laugharne J, Rangarajan N, et al. Tardive dyskinesia, lipid peroxidation, and sustained amelioration with vitamin E treatment. *Int Clin Psychopharmacol* 1993;8:151–3.
- [52] Arvindakshan M, Ghate M, Ranjekar PK, et al. Supplementation with a combination of  $\omega$ -3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. *Schizophr Res* 2002 (in press).
- [53] Roy D, Pathak DN, Singh R. Effects of chlorpromazine on the activities of antioxidant enzymes and lipid peroxidation in the various regions of aging rat brain. *J Neurochem* 1984;42:628–33.
- [54] Shivkumar BR, Ravindranath B. Oxidative stress and thiol modification induced by chronic administration of haloperidol. *J Pharmacol Exp Ther* 1993;265:1137–41.
- [55] Jedding I, Evans PJ, Akanmu D, et al. Characterization of the potential antioxidant and pro-oxidant actions of some neuroleptic drugs. *Biochem Pharmacol* 1995;49:359–65.
- [56] Subramanyam B, Rollema H, Wolf T, et al. Identification of a potentially neurotoxic pyridinium metabolite of haloperidol in rat. *Biochem Biophys Res Commun* 1990;166:238–44.
- [57] Horrobin DF. The effects of antipsychotic drugs on membrane phospholipids—a possible novel mechanism of action of clozapine. In: Peet M, Glen I, Horrobin D (eds). *Phospholipid spectrum disorders in psychiatry*. Lancashire: Marius Press; 1999. p. 113–7.

- [58] Peet M, Horrobin DF. A dose-ranging exploratory study of the effects of ethyl-EPA in patients with persistent schizophrenic symptoms. *J Psychiatr Res* 2002;36:7–18.
- [59] Parikh V, Khan MM, White JR, et al. Atypical antipsychotics such as risperidone and clozapine do not induce the oxidative stress and the lipid peroxidation similar to haloperidol in rats. *Biol Psychiatry* 2002;51:184S–5S.
- [60] Thomas EA, Danielson PE, Nelson PA, et al. Clozapine increases apolipoprotein D expression in rodent brain: towards a mechanism for neuroleptic pharmacotherapy. *J Neurochem* 2001;76:789–96.
- [61] Khan MM, Parikh V, Mahadik SP. Effects of chronic exposure of antipsychotics on apolipoprotein D in rat brain. *Biol Psychiatry* 2002;51:168S.
- [62] Thomas EA, Dean B, Pavey G, et al. Increased CNS levels of apolipoprotein D in schizophrenic and bipolar subjects: implications for the pathophysiology of psychiatric disorder. *Proc Natl Acad Sci U S A* 2001;98:4066–71.
- [63] Mahadik SP, Khan MM, Evans DR, et al. Elevated plasma levels of apolipoprotein D in schizophrenia and implications for its treatment outcome. *Schizophr Res* 2002;58:55–62.
- [64] Kaiya H, Nishida A, Imai A, et al. Accumulation of diacylglycerol in platelet phosphoinositides turnover in schizophrenia: a biological marker of good prognosis? *Biol Psychiatry* 1989;26:669–76.
- [65] Essali MA, Das R, de Belleruche J, et al. The platelet polyphosphoinositide system in schizophrenia: the effects of neuroleptic treatment. *Biol Psychiatry* 1990;28:478–87.
- [66] Yao JK, Yasaei P, van Kammen DP. Increased turnover of platelet phosphatidylinositol in schizophrenia. *Prostaglandin Leukotr Essential Fatty Acids* 1992;46:39–46.
- [67] Hudson CJ, Young TL, Li PP, et al. CNS signal transduction and pathophysiology and pharmacotherapy of affective disorder and schizophrenia. *Synapse* 1993;13:278–93.
- [68] Braff D. Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull* 1993;19:233–60.
- [69] Khan A, Khan SR, Leventhal RM, et al. Symptom reduction and suicide risk among treated with placebo in antipsychotic clinical trials: an analysis of the Food and Drug Administration database. *Am J Psychiatry* 2001;158:1449–54.
- [70] Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* 1994;151:1409–16.
- [71] Fenton WS, Hibbelin J, Knable M. Essential fatty acids, lipid membrane abnormalities, and the diagnosis of schizophrenia. *Biol Psychiatry* 2000;47:8–12.
- [72] Fenton WS, Dickerson F, Boronow J, et al. A placebo controlled trial of omega-3 fatty acids (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001;158:2071–4.
- [73] Tsay HJ, Wang P, Wang SL, et al. Age-associated changes of superoxide dismutase and catalase activities in the rat brain. *J Biomed Sci* 2000;7:466–74.
- [74] Vaddadi KS, Courtney P, Gilleard CJ, et al. A double-blind trial of essential fatty acids supplementation in patients with tardive dyskinesia. *Psychiatry Res* 1989;27:313–23.
- [75] Peet M, Brind J, Ramchand CN, et al. Two double blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001;49:243–51.
- [76] Rafalowska U, Liu G-J, Floyd RA. Peroxidation induced changes in synaptosomal transport of dopamine and gamma-aminobutyric acid. *Free Rad Biol Med* 1989;6:485–92.
- [77] Schwartz RD, Skolnick P, Paul SM. Regulation of gamma-aminobutyric acid/barbiturate receptor gated chloride ion flux in brain vesicles by phospholipase A2: possible role of oxygen radicals. *J Neurochem* 1988;50:565–71.
- [78] Mahadik SP, Evans D, Lal H. Oxidative stress and role of antioxidant and  $\omega$ -3 essential fatty acid supplementation in schizophrenia. *Progr Neuropsychopharmacol Biol Psychiatry* 2001;25:263–93.
- [79] Adler LA, Peselow E, Rotrosen J, et al. Vitamin E treatment of tardive dyskinesia. *Am J Psychiatry* 1993;150:1405–7.

- [80] Adler LA, Rotrosen J, Edson R, et al. Vitamin E treatment for tardive dyskinesia. *Arch J Psychiatry* 1999;56:836–41.
- [81] Mahadik SP, Gowda S. Antioxidants in the treatment of schizophrenia. *Drugs Today* 1996;32:1–13.
- [82] Mahadik SP, Evans DR, Terry A, et al. Neuroprotective action of atypical antipsychotics in schizophrenia: improved cognitive performance and underlying mechanism of action. *Schizophr Res* 2001;49:94.