Optimal Dosing for Schizophrenia

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Introduction

Neuroleptics are tranquillizers (major sedatives) that block brain neuron transmission at the receptor level.[1] Neuroleptics can be useful during acute episodes of schizophrenia but should be prescribed with the intention of stabilizing the patient, not with the intention of long-term tranquillization. The human body was not made to function in a tranquillized state. I do not know of any physician willing to try this regimen themselves for a prolonged period of time. As this article will discuss, neuroleptic medication can become problematic, not only due to its side-effects, but also because it can cause a psychosis on its own with cognitive deficits. This does not diminish its usefulness in the field to address psychotic symptoms in times of need. Neuroleptics are a valuable asset in nutritional adjunct therapy for schizophrenia.

Safe therapeutic doses of medication that achieve a desirable effect are considered optimal. This basic principle of 'optimal dosing' holds true for nutritional supplements and prescribed drug medication. Schizophrenic patients treated with an optimal nutritional adjunct therapy improve at a consistent rate. In this article I have referenced several studies and several peer reviewed journal articles that describe the effectiveness of this treatment. Over 50 years of clinical experience from practitioners in the field also attest to the viability of nutritional adjunct therapy. Effectiveness is dependent on the severity and chronicity of symptoms. As a practitioner, initial signs of improvement become apparent in subtle ways. It is not uncommon to receive first-hand reports from parents that their son or daughter has started to smile, express appropriate emotions, and wants to help around the house. The 'negative symptoms' of schizophrenia diminish and the patient starts getting along better with family, friends, and society. These first signs of improvement indicate that you have achieved optimal nutritional doses. In general, improvement will continue in a consistent manner with both 'positive' and 'negative' symptom alleviation. However, the benefits of nutritional therapy plateau when the patient maintains previous 'stabilized' neuroleptic doses. Despite showing signs of consistent improvement, the patient reaches a point of inflection and, if they maintain their previous 'stabilized' neuroleptic dose, improvement does not continue. They remain improved but often they are not well enough to enter a vocation or career. The skilled practitioner, however, recognizes that there is room for improvement. As this article will describe, continued improvement is observed in those patients that maintain the lowest effective/optimal dose of neuroleptic. For many patients, this dose is much lower than their previous 'stabilized' dose. Some patients are able to maintain a token dose of neuroleptic while some are able to withdraw completely. It is important to initiate a slow careful titration of neuroleptic dosing while monitoring symptoms with regular patient follow-ups. If necessary, inter-practitioner collaboration can be implemented at this stage.

The Optimal Neuroleptic Dose to Maintain Brain Structure Integrity

Brain structure loss is one of the biggest and most significant 'side-effects' of neuroleptic treatment. Maintaining brain structure is an important part of the nutritional protocol for schizophrenic pathology.[2] The natural course of this disease and neuroleptic exposure are both associated with brain structure compromise.

Increased lateral and third ventricle size (suggesting atrophy in adjacent brain

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structures) may precede the onset of schizophrenia.[3,4] A recent 2002 review by E. Fuller Torrey reports on various studies suggesting significant ventricular hypertrophy in schizophrenics never treated with neuroleptics (neuroleptic-naïve) compared to matched normal controls.[5] Torrey reports less conclusively of various studies suggesting abnormal volumes in the basal ganglia (caudate, putamen, globus pallidus), thalamus, frontal/parietal cortex, medial temporal structures, latero-dorsal prefrontal gray matter, entorhinal cortex, septum pellucidum, and the corpus callosum of neuroleptic-naïve schizophrenic patients versus normal controls.

Abnormal brain structure changes have been reported in conjunction with neuroleptic-treated schizophrenic patients. The risk of sub-cortical (caudate, putamen, and thalamic) brain structural loss (atrophy) seems to increase by 6.4% for every 10 g of neuroleptic (chlorpromazine equivalents) prescribed.[6] The review by Torrey mentioned above does not compare neuroleptic-naïve schizophrenic patients with neuroleptic-treated schizophrenic patients. A research review is needed to compare the degree of brain atrophy and hypertrophy in neuroleptic-naïve versus neuroleptic-treated schizophrenic patients. I found only two studies comparing these patient cohorts.

Gur et al. report on increased volumes (hypertrophy) of basal ganglia (putamen, globus pallidus, and caudate) and thalamic structures in a study comparing 75 neuroleptic-treated schizophrenic patients, 21 neuroleptic-naïve schizophrenic patients, and 128 healthy controls.[7] Of the 75 neuroleptic-treated patients, 48 received typical neuroleptics and 27 received both typical and atypical neuroleptics. The neuroleptic-treated group reported hypertrophy in the putamen and globus pallidus versus the neuroleptic-naïve and healthy controls. The higher the dose of typical neuroleptic the greater the caudate, putamen, and thalamic hypertrophy. The hypertrophic state reported here represents structural loss of functional brain tissue with decreased neuronal pruning, synaptic adaptations, and striatal activation. This study also reports on atypical neuroleptics and associated thalamic hypertrophy.

Chakos et al. report on caudate hypertrophy in a study comparing 29 first-episode schizophrenic patients given standardized neuroleptic regimens for 18 months versus 10 healthy controls.[8] This study reports a 5.7% increase in caudate volume during the 18 months of neuroleptic treatment. Greater hypertrophy was reported in patients given larger doses of neuroleptic. Hypertrophy reported here represents structural loss of functional brain tissue.

Brain cells cannot regenerate and any loss of functional tissue, from atrophic or hypertrophic changes, represents a substantial irreversible deficit. This is one area where nutritional support is very useful.[2]

Anti-psychotic medications are tranquillizers or major sedatives designed to block nerve transmission in the brain. Most neuroleptics block a select group of neurotransmitter receptors (typically dopamine receptors; but also glutamate, acetylcholine, serotonin, GABA, and histamine receptors) in the brain.[9] Since nerve receptors are complex networks spreading all over the brain, these drugs often block unwanted nerve pathways. In pharmacology, it is said that these drugs have poor specificity for their target. Many drugs have poor specificity and this is the main cause of side-effects. When neuroleptics target unwanted brain pathways many undesirable and debilitating side-effects can occur. These include unwanted muscle movements (extrapyramidal symptoms), diabetes, loss of libido, weight gain and tardive dyskinesia. For a full list of side-effects refer to the Compendium of Pharmaceuticals and Specialties (CPS) which will describe the side effects and indications of specific drugs.[1] Some neuroleptics can have fatal

consequences such as agranulocytosis, associated with clozapine use, and neuroleptic malignant syndrome, associated with atypical neuroleptics. Neuroleptic withdrawal is also associated with side-effects.

Neuroleptic withdrawal is done routinely in psychiatric and general practice, usually to start a patient on a different neuroleptic when they are considered refractory to initial treatment. It is well known that the side effects of neuroleptic withdrawal are created by chemical and receptor changes initiated by the drug. In these cases it is common for psychotic symptoms to re-emerge. When some patients are withdrawn from neuroleptics, the receptors, starved for neurotransmitter (especially dopamine) stimulation, compensate by becoming supersensitive causing a rebound psychosis. In some cases denervation supersensitivity occurs resulting in irreversible loss of brain tissue. The concept of denervation supersensitivity has emerged recently as a potential mechanism for neuroleptic-induced (or iatrogenic) brain tissue loss and extrapyramidal side-effects in schizophrenic patients.[10-15]

Neuroleptic Management

Conventional psychiatry in the 1950s adopted the use of neuroleptics. People with schizophrenia responded to chlorpromazine (the first neuroleptic; actually an antihistamine) and what followed was the early release from hospitals of patients considered 'stabilized'. The relapse rate was high and people with schizophrenia had to be re-admitted and released again; hence the 'revolving door' era and resultant economic burden.[16,17] Neuroleptic treatment and prognosis remains encouraging because it is a form of palliation that suppresses symptoms. Neuroleptic management is considered by most people the only useful biochemical treatment for people with schizophrenia, the corollary of which implies that there is no hope unless neuroleptic compliance is maintained. Neuroleptics work quickly which is a good feature. There are many cases when tranquillizing a patient becomes useful. The aim however, should not be long-term management with a neuroleptic. In neuroleptic management of chronic and first-episode schizophrenia, maximum symptomatic improvement is thought to occur in the first 6 months and, as the disease progresses the effectiveness seems to diminish.[18]

Continued use of neuroleptics in the management of schizophrenia becomes problematic not only due to drug side-effects but also because of their ability to cause psychosis on their own- a psychosis clearly distinguishable from the natural psychosis of the disease.[19-23] Cognitive deficits are also associated with neuroleptic use.[24-27] Dr. Meyer Gross, eminent psychiatrist in England, claimed in the 1950s that neuroleptic drugs produced another psychosis in addition to the natural disease psychosis.[19,28] As time progresses the patient experiences an emergence of drug-psychosis symptoms and apathy sets in. At this stage many patients become compliant and dependent on antipsychotic medication. It is estimated that the natural recovery rate of schizophrenia without drug administration approximates 50% versus 10% with those who recover from drug administration alone.[6] Neuroleptics should therefore be used only when essential, with one neuroleptic at a time, with minimal doses that can gradually be withdrawn while the nutritional therapy addresses the biochemical cause of schizophrenic pathology. Multiple neuroleptic administration is a common practice but it can be considered experimental at best. The pharmacokinetics and pharmacodynamics of multiple neuroleptic dosing have not been well researched and I fail to find a controlled study to support their use.[29-32]

The current practice of administering neuroleptic medication "is primarily grounded on the subjective clinical experi-

ence of practitioners and not on scientifically derived data. This uncontrolled, empirical approach dates from initial reports by Delay et al. (1953)".[33] Neuroleptic dosing schedules remain ambiguous and, increasingly, more clinical evidence is pointing to the lack of benefit of high-dose neuroleptic treatment–substantiated by neural transmission studies and relapse data.[33] In a meta-analysis by Hegarty et al. in 1994 it was noted that iatrogenic burden placed on schizophrenic patients 'today' is more prominent than it was a 100 years ago.[34] Carpenter et al. have claimed dose reduction feasible in patients on maintenance neuroleptic therapy.[35] As a general rule, schizophrenic symptoms are worsened when neuroleptic doses are too high, too low, or quickly withdrawn. This is especially true with neuroleptics that have such a vast array of severe, debilitating, and life threatening side effects.[1]

Anti-depressants are often used in schizophrenic patient management if depression is a major component of the symptomology.[36] This can be useful especially in paranoid schizophrenia. Dr. Abram Hoffer notes that it is difficult to find a cheerful paranoid schizophrenic. He has found good results with clomipramine.[36]

An Evidence-based Look at Nutritional Adjunct Therapy

In the year 2000, the Metropolitan King County Council, in the state of Washington, passed legislation to allow performance monitoring of all psychiatric care, conventional or otherwise.[16] This allowed them to assess the need to make changes in the health care system. This evidence-based model would best serve the needs of schizophrenic patients abroad and is mentioned here as a catalyst and template for future research endeavours between conventional psychiatrists and complementary medical practitioners.

It is important to review the findings of research done on neuroleptic-treated schizophrenics given nutritional adjuncts involving vitamin B_3 with neuroleptic withdrawal in those cases with clear indication of continued improvement. Six double-blind placebo controlled trials on schizophrenic patients have been done using this method.[37] For the duration of these trials, all schizophrenic patients were able to safely maintain prescribed neuroleptic medication. It was found that some patients required a skilful combination of both neuroleptics and nutritional treatment while some patients did better on nutritional treatment alone.

The B_3 therapy is discussed in detail in various journals and literature sources which I will list as a review of nutritional orthomolecular psychiatry along with a review of its effectiveness and the mechanisms of action.[19,36-54] The six double blind trials done by Hoffer et al. were the first double blind placebo controlled trials ever done in the history of psychiatry.[54]

Today, many patients are maintained well on low neuroleptic doses. Thousands of cases have been treated with this vitamin B_3 nutritional adjunct method. Nutritional adjunct therapy has expanded to include supplements in addition to vitamin B_3.[2] Nutritional management of schizophrenia is associated with independence and increased integration into the community, family unit, and workforce (paying income tax).

In the clinical management of psychiatric cases it is best to gauge patient symptoms using outcome measures and unbiased objective clinical impression. This is a key part of evidence-based medicine. The patient's subjective report and the practitioner's objective clinical impression (Global Assessment of Functioning, GAF) are important especially when used in combination with valid and reliable outcome measures such as the Positive and Negative Symptom Scale (PANSS), Experiential World Inventory (EWI), or the Hoffer-Osmond Diagnostic (HOD). The HOD test is a reliable and valid subjective outcome measure used to gauge symptoms of behaviour as defined by Karl Menninger categories of perception, mood, and thinking which together define behaviour.[55,56]

The Key Ingredient, Niacin: How Does it Work?

The various forms of vitamin B_3 include niacin, niacinamide, inositol hexaniacinate, and NADH. Vitamin B_3 can limit the conversion of norepinephrine to epinephrine (adrenaline). Excess adrenaline or excess catecholamines such as dopamine (implicated in the dopamine hypothesis of schizophrenia) are problematic as they can oxidize and form endogenous toxins. The brain with similar local reactions may fail to store excess catecholamines, a job normally reserved for neuromelanin, and hence allow free circulation of neurotoxins.[45,49,57] B_3 dependent pathways in the body vent the biochemistry of the body away from the formation of oxidized catecholamines and toxic indoles which might, under certain circumstances, contribute to synaptic deletion. Abnormalities in this neuromelanin storage pathway may be considered a causative factor in schizophrenic (and Parkinson's) pathology. The 'adrenochrome hypothesis' was the first biochemical theory of schizophrenia described in the history of psychiatry.[45] Drs. Abram Hoffer and Humphry Osmond spearheaded this nutritional approach. Dr. Abram Hoffer, M.D., Ph.D., N.D.(honorary), has treated over 5,000 patients with this approach and currently practices in Victoria, B.C., Canada.

The nutritional need/dependency versus deficiency (a less dependent state) for B_3 may indeed exceed the need to address any other nutritional metabolic compromise in schizophrenia. The optimal dose of vitamin B_3 (excluding the NADH form) for schizophrenia, as determined over the past 50 years by clinical trial, is about 3,000 mg per day but some patients require as much as 12,000 mg per day depending on response. Some patients also do well on smaller doses. Vitamin B_3 is considered safe- as described in full, in a recent review on vitamin B_3 administration in the *Journal of Orthomolecular Medicine*, Special Issue, Volume 18 (3/4), pages 146-160. Time-released forms of vitamin B_3 are not considered safe.

Nutritional therapy needs to be maintained for at least five years and many patients need longer durations of nutritional supplementation.[36] The duration of nutrient therapy should carry on until the likelihood of relapse seems unlikely. Chronic patients are not as responsive to nutritional regimens as are acute cases and not everyone will get 'well'. Prognostic outcomes of nutritional therapies for schizophrenia are described in the literature.[2,37] In most cases, if patients are taken off prescribed nutrients during a hospital admission they deteriorate. Many patients are thus demanding that they maintain their supplement protocols during hospitalizations.[36]

With niacin administration there is an interesting side-effect of longevity. The Mayo Clinic found significant reductions in mortality in subjects with high baseline cholesterol who used niacin alone.[58,59] Niacin also plays a role in the essential fatty acid metabolism of the brain, processes of which are disrupted in schizophrenia. Together, vitamin B_3 and C (ascorbic acid) are centrally active in the brain as "niacinamide acts on the diazepine receptors, while ascorbic acid acts on the dopamine receptors, as do Haldol and other [neuroleptics or] tranquillizers".[43]

Summary

The aim of nutritional management in schizophrenia is not to offer a cure-all replacement for standard treatment. Signs of clinical improvement are best determined with outcome measures before and during nutritional adjunct therapy. If monitored carefully, neuroleptic withdrawal can be done with minimal negative side-effects when nutritional adjuncts are used in schizophrenic patients showing consistent improvement. Slow careful withdrawal is extremely important to avoid rebound psychosis. This neuroleptic withdrawal concept is an optimal dosing principle associated with improved patient response.

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