REVIEW ARTICLE

CNS Drugs 2003; 17 (1): 47-62
1172-7047/03/0001-0047/$30.00/0

© Adis International Limited. All rights reserved.

Oxidative Mechanisms and Tardive Dyskinesia

James B. Lohr, Ronald Kuczenski and *Alexander B. Niculescu*

Department of Psychiatry, University of California San Diego, San Diego, California, USA

Contents

Abstract

Tardive dyskinesia has been and continues to be a significant problem associated with long-term antipsychotic use, but its pathophysiology remains unclear. In the last 10 years, preclinical studies of the administration of antipsychotics to animals, as well as clinical studies of oxidative processes in patients given antipsychotic medications, with and without tardive dyskinesia, have continued to support the possibility that neurotoxic free radical production may be an important consequence of antipsychotic treatment, and that such production may relate to the development of dyskinetic phenomena.

In line with this hypothesis, evidence has accumulated for the efficacy of antioxidants, primarily vitamin E (α-tocopherol), in the treatment and prevention of tardive dyskinesia. Early studies suggested a modest effect of vitamin E treatment on existing tardive dyskinesia, but later studies did not demonstrate a significant effect. Because evidence has continued to accumulate for increased oxidative damage from antipsychotic medications, but less so for the effectiveness of vitamin E, especially in cases of long-standing tardive dyskinesia, alternative antioxidant approaches to the condition may be warranted. These approaches may include the use of antioxidants as a preventive measure for tar-

dive dyskinesia or the use of other antioxidants or neuroprotective drugs, such as melatonin, for established tardive dyskinesia.

1. Background to the Hypotheses of Tardive Dyskinesia

It is now over 40 years since the initial descriptions of tardive dyskinesia were made in the late 1950s and early 1960s.[1] During that time, the incidence of tardive dyskinesia grew to near epidemic proportions in patients treated with antipsychotics. In the past few years, the incidence of tardive dyskinesia has finally appeared to be waning, largely as a result of the introduction of newer second-generation (atypical) antipsychotic agents, some of which have a much reduced propensity to cause tardive dyskinesia.[2] However, our enthusiasm at this apparent reduction in tardive dyskinesia should be limited, because many patients are still affected by the condition, and there are groups of patients, such as older individuals, for whom the development of tardive dyskinesia remains a significant problem.[3,4]

What causes tardive dyskinesia? The most popular hypothesis throughout the 1980s was that tardive dyskinesia was the result of a secondary brain response to drugs that block activity of the neurotransmitter dopamine on the postsynaptic membrane in certain brain regions related to motor control. In response to this chronic dopaminergic blockade, the brain produces more dopamine receptors, and probably receptors that respond to lower levels of dopamine as well.[5,6] It was considered that this 'supersensitivity' of dopamine receptors in brain regions involved in the modulation of movement – the extrapyramidal motor system in particular – could result in a hyperdopaminergic state, manifesting clinically as a dyskinesia, a disorder characterised by excessive involuntary movement. This hypothesis became known as the 'dopamine supersensitivity hypothesis' of tardive dyskinesia.[7]

Although this mechanism of dopamine supersensitivity secondary to chronic dopaminergic blockade clearly occurs, there are reasons to think that it may not be the exclusive cause of tardive dyskinesia. First of all, preclinical studies in rodents indicate that dopamine supersensitivity appears to be a universal response to the administration of dopamine receptor–blocking drugs such as antipsychotics. However, tardive dyskinesia develops in only a proportion of patients, on average 20 to 25%, treated with first-generation antipsychotic medications. The time course for the development of supersensitivity – in the range of days to weeks – also does not match that for tardive dyskinesia, which develops after months to years. With increasing age, there is a reduction in the ability of the brain to mount a dopamine supersensitivity response, yet the incidence of tardive dyskinesia actually increases with age. Finally, when the offending antidopaminergic agent is withdrawn, supersensitivity diminishes and dopamine receptor numbers return to baseline, whereas in tardive dyskinesia, between one-third and one-half of cases appear to be essentially irreversible (for reviews, see Lohr and Jeste[8] and Sachdev[9]).

It was because of these problems with the dopamine supersensitivity hypothesis that Cadet and Lohr[10] proposed an alternative pathophysiological mechanism for tardive dyskinesia in the late 1980s. Fibiger and Lloyd[11] in 1984 suggested that, through some mechanism, persistent tardive dyskinesia may result from damage to γ-aminobutyric acid (GABA)-ergic neurons in the basal ganglia. Cadet and Lohr[10] also considered that there must be a neurotoxic process occurring in individuals treated with antipsychotics to explain the potential irreversibility of the condition. This line of reasoning has become known as the 'neuronal degeneration hypothesis' of tardive dyskinesia.[12,13]

Although there are a number of possible mechanisms for neuronal degeneration, many of which interact with one another (including excitotoxicity and other mechanisms,[14] which are reviewed in section 5), it was considered that a mechanism based on the formation of free radicals – reactive chemical species with a single unpaired electron –

© Adis International Limited. All rights reserved.

might be involved. It was known that dopamine metabolism could cause the creation of free radicals, and that dopaminergic blockade could cause a secondary increase in dopamine production and metabolism. Also, oxygen radical production offered an explanation for some of the other clinical characteristics of tardive dyskinesia that were problems for the dopamine supersensitivity hypothesis. Increased free radical production can produce damage that is both reversible and irreversible, which have been long-observed clinical characteristics of tardive dyskinesia. Individual variation in the ability to handle increased free radical generation could account for why some people develop tardive dyskinesia and others do not.[8,10] Oxidative damage may increase with age, offering a potential explanation for why tardive dyskinesia increases with age.[15,16]

Other putative risk factors for tardive dyskinesia, such as alcohol abuse, diabetes mellitus and being an older woman (i.e. risk of tardive dyskinesia due to lack of an antioxidant effect of estrogens),[17,18] could potentially also relate to increased free radical burden.[19-22] Another reported risk factor for tardive dyskinesia, the repeated starting and stopping of antipsychotic medication, is also consistent with a free radical mechanism, in which there may be bursts of free radical production related to dopamine hyperactivity following the initiation of an antipsychotic, but with subsiding free radical production over time.[23] Finally, a slow accrual of oxidative damage can take months to years to increase to the extent where there may be an observable clinical effect.[10,15] This line of thought became the 'free radical hypothesis' of tardive dyskinesia.

This does not mean that the dopamine supersensitivity hypothesis is not important in the pathogenesis of dyskinesias. We considered that dopamine supersensitivity could very well pertain to the development of dyskinetic phenomena, but likely was not enough to explain tardive dyskinesia proper, especially chronic persistent tardive dyskinesia. Instead, the supersensitivity hypothesis seemed a reasonable explanation for the development of antipsychotic withdrawal–emergent dyskinesias,[24,25] which occur within several weeks of the cessation or decrease in antipsychotic medication and are time limited, generally disappearing within 2 months. The time course of these dyskinesias, which can be phenomenologically indistinguishable from tardive dyskinesia, appears to fit better with the supersensitivity hypothesis.[8] For example, it would make sense that a secondary increase in dopamine receptors after dopaminergic blockade would be associated with a clinical manifestation of dyskinesia when the antidopaminergic agent was withdrawn, because then all additional receptors would be unblocked and would lead to increased dopaminergic transmission. But, after withdrawal of the antipsychotic agent, there would be a compensatory decrease in receptors over time, corresponding with an attenuation of the dyskinesia. This would also account for the common observation that tardive dyskinesia can worsen after antipsychotic dosage reduction or withdrawal, but then reduce with time.[8] In effect, there are two dyskinesias here, tardive dyskinesia and a withdrawal dyskinesia, which clinically look the same (both involving primarily the lower facial and distal extremity musculature[1]), but which may be underlined by somewhat different pathophysiologi-

1 The pathophysiological or pathoanatomical reason why tardive dyskinesia in most individuals primarily involves the lower facial musculature as well as the distal extremities is currently unknown. It is therefore difficult to discuss how free radical–induced toxicity may relate to the specific anatomical distribution of the syndrome. Although one is tempted to speculate that certain brain regions may be more vulnerable than others to the tardive dyskinesia–causing effects of antipsychotics, it is not known what that vulnerability might be. The anatomical regions affected by tardive dyskinesia seem to be dedicated to complex movements, such as those subserving communication functions as with speech and gesture,[8] but again this does not necessarily imply a specific pathophysiological mechanism for tardive dyskinesia. Although it is possible that brain regions involved in the control of complex motor functions may be at greater risk of free radical–induced damage than other regions, there is to the authors' knowledge no direct evidence for this conjecture.

© Adis International Limited. All rights reserved.

cal mechanisms and degrees of severity and reversibility.

In the remainder of this review, we will focus on evidence for the free radical hypothesis of tardive dyskinesia, both from a preclinical and clinical perspective, as well as on studies of the use of antioxidants in the treatment of tardive dyskinesia. We will also discuss possible relationships between free radical mechanisms and other neurodegenerative mechanisms. To begin, we will present briefly the free radical hypothesis of tardive dyskinesia in a more detailed form.

2. The Free Radical Hypothesis of Tardive Dyskinesia

2.1 Free Radicals in Biological Systems

For an overview of free radicals, readers are referred to Halliwell and Gutteridge.[26] As mentioned above, free radicals are highly reactive chemical species that contain an unpaired electron. In animal systems, oxygen radical formation is particularly common, to a large extent because it is through the chemical reduction of oxygen that much of the energy is supplied for the vast and complex cellular chemical reactions occurring throughout the body. Unlike simple inorganic oxidative reactions, such as the combustion of carbon, which release large amounts of heat and light, living tissue has developed ways of efficiently harnessing this energy and pulling off the energy of oxidation piecemeal. The electron transport chain of mitochondria is an excellent example of how this occurs, where the energy of oxidation is sequentially parcelled into high-energy phosphate bonds in chemicals such as adenosine triphosphate (ATP), which can then travel to various places in the cell and donate this energy in defined packets to run various chemical reactions. However, free radicals are produced during this process. As summarised by Acuna-Castroviejo et al.,[27] 'although ideally all the oxygen should be reduced to water by a four-electron reduction reaction driven by the cytochrome oxidase, under normal conditions a small percentage of oxygen may be reduced by one, two or three electrons only, yielding superoxide anion ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2) and the hydroxyl radical, respectively. The main radical produced by mitochondria is $O_2^{-\bullet}$ and the intramitochondrial antioxidant systems should scavenge this radical to avoid oxidative damage, which leads to impaired ATP production'.

This energy transfer in the electron transport chain, and in many other reactions in the cell, occurs through the handing off of electrons from one substance to another. In this process, free radicals frequently occur, in which an electron exists in an unpaired state. This is generally a very unstable state for a molecule. The readiness of a free radical to transfer or share this unpaired electron with another molecule is what makes the free radical highly reactive.

It can be seen that free radical production, when controlled, is very important for cells. It allows for the extraction of parcels of usable energy for metabolism. It is also useful for the dismantling of substances, because free radicals can be employed to pull apart large chemical structures, such as proteins and lipids, into their more basic components. Thus, free radical mechanisms are important for the activity of lysosomes, in which large macromolecular structures can be dismantled into their building blocks. This is very important for obtaining energy from foodstuffs that have been ingested or invaginated, as well as for the destruction of pathogens.

Without careful control, oxidative processes can also cause damage to the organism itself. Cells are literally playing with fire, and the fire can quickly get out of control. Nowhere is this clearer than in the membrane structures of cells. Here, an errant free radical contacting a membrane fatty acid, particularly a polyunsaturated fatty acid with many double bonds that can be oxidised, can touch off a chain reaction of free radical production called the lipid peroxidation cascade. One unpaired electron-containing fatty acid gives rise to two, which give rise to four, and so on. These reactions literally spread across the membrane and can damage its integrity, as well as causing alter-

© Adis International Limited. All rights reserved.

ations to the massive numbers of proteins that are located within the membrane, including receptor proteins. Cellular communication can be disrupted because of this.[26] Cells can actually die if holes open up in the membrane, compromising the integrity of the cell in particular and causing cell destruction, either directly or by allowing calcium ions to flow in, which can activate apoptotic mechanisms.

Thus, cell membranes are extremely vulnerable to oxidative processes. The presence of transition metals, such as iron, copper and manganese, also leads to increased vulnerability. Transition metals, and substances that are not themselves radicals, such as H_2O_2, can give rise to extremely highly reactive radicals, such as the hydroxyl radical. Indeed, transition metal atoms readily accept electrons and are therefore frequently found in enzymes that catalyse reactions through which free radicals are formed or destroyed. Thus, one of the major enzymes involved in free radical chemistry – superoxide dismutase (SOD), which catalyses the formation of H_2O_2 from $O_2^{-\bullet}$ (where $\bullet$ indicates the presence of an unpaired electron) exists in two forms, both of which contain transition metals: manganese in the case of MnSOD, which occurs in mitochondria; and copper and zinc in Cu/ZnSOD, which is cytosolic.

How does the body defend itself against free radical–induced damage? There are essentially two mechanisms.[26] One involves the use of chemical antioxidants, which are substances that can render free electrons harmless through a variety of mechanisms. For example, the antioxidant vitamin E (α-tocopherol) works by accepting an electron and becoming a vitamin E radical, which is much less reactive than other free radicals. The other mechanism involves enzymes that catalyse reactions in which free radicals or free radical–producing substances are altered to form nonradical structures. Examples here include the enzyme SOD mentioned above, as well as the enzymes catalase (CAT) and glutathione peroxidase (GSH-Px), both of which catalyse the formation of water and oxygen from H_2O_2.

2.2 Free Radicals in the Brain

The brain is particularly vulnerable to free radical damage for several reasons.[28-31] First, it uses an enormous amount of energy, receiving roughly 20% of the cardiac output of oxygenated blood. Second, it contains huge amounts of polyunsaturated fatty acids, providing a large arena for activity of lipid peroxidation cascades. Certain regions of the brain that are involved in motor function, such as the basal ganglia, are rich in transition metals as well.

Another point of vulnerability concerns areas of the brain that contain large amounts of catecholamines, such as dopamine. The metabolism of dopamine is associated with free radical production through several mechanisms. One is that dopamine molecules may auto-oxidise to become dopamine quinones, which are free radicals themselves. Auto-oxidation may also give rise to $O_2^{-\bullet}$. A second mechanism is that one of the major enzymes involved in dopamine metabolism, monoamine oxidase (MAO), produces H_2O_2 instead of water, a very unusual situation. This H_2O_2 can be readily cleaved, especially in the presence of transition metals, forming two molecules of the most highly reactive oxygen radical of all: the hydroxyl radical.[10,28-31]

2.3 Free Radicals and Antipsychotic Medications

It is against the preceding backdrop that we can understand the development of the free radical hypothesis of tardive dyskinesia. Antipsychotic medications, by blocking dopamine receptors, can cause a secondary increase in dopamine synthesis and a corresponding increase in dopamine metabolism. The latter can be associated with increased free radical formation by MAO, which forms H_2O_2 (which, in the presence of transition metals, can produce highly reactive hydroxyl radicals); increased dopamine metabolism can also result, through auto-oxidation, in the increased formation of dopamine quinones and $O_2^{-\bullet}$. When this occurs in areas of the brain where there are large amounts

© Adis International Limited. All rights reserved.

of oxygen delivery, polyunsaturated fatty acids and transition metals – such as the basal ganglia – the stage appears to be set for excess free radical production, which can overwhelm antioxidant brain defences, slowly producing damage.[28] Also, antipsychotic medications themselves may be associated with an increase in transition metals in the basal ganglia,[32,33] and it is possible that some antipsychotic drugs, such as haloperidol, may be directly toxic through a free radical–related mechanism or through the creation of reactive oxygen species in mitochondria,[34,35] as reviewed in section 3.

3. Preclinical Studies of Oxidative Damage with Antipsychotic Medications

Preclinical studies of the hypothesis that antipsychotics may cause damage through oxidative mechanisms fall into two broad groups. First, there are studies in which antipsychotic medications are given to animals or used in cell cultures; oxidative products are then measured and antioxidants are also possibly administered to see if there is an alteration in these oxidative products. Second, there are studies that concern the use of oxidative measurements and antioxidant interventions in animal models of tardive dyskinesia.

3.1 Antipsychotic-Induced Increases in Oxidative Damage

Murthy et al.[36] and Cadet and Perumal[37] reported evidence of increased membrane lipid peroxidation and impairment in antioxidant enzyme activity in animals treated with antipsychotic medications. The administration of antipsychotics in rodents has also been associated with decreased levels of glutathione in the brain, particularly the striatum,[38,39] and evidence of increased free radical activity and glutamate transmission.[40]

Recently, cell culture studies by several groups of investigators suggested that haloperidol and its metabolites might be directly toxic to neurons. Behl and colleagues[41] reported a direct toxic effect of haloperidol on primary hippocampal neurons, C6 glioma cells and NCB20 cells, although this damage appeared to be through a necrotic rather than an apoptotic mechanism. Vitamin E prevented this damage.

Sagara[34] studied the effect of haloperidol on rat primary cortical neurons and on a mouse hippocampal cell line (HT-22). This research suggested that haloperidol caused an increase in reactive oxygen species generated by the mitochondria, but not through metabolism of catecholamines by MAO. The investigator reported that vitamin E and β-estradiol (which also has antioxidant properties) protected against the haloperidol-induced changes.

Galili-Mosberg et al.[35] administered haloperidol and metabolites to cell cultures of murine neurons (PC-12) and determined that cells died through an apoptotic mechanism, rather than a necrotic one. Further, the researchers found that antioxidants, including vitamin E, were effective in attenuating this cell damage. (To our knowledge, although there are very few neuropathological studies of tardive dyskinesia in humans, none has reported significant gliosis, which suggests an apoptotic rather than a necrotic mechanism.) This was also one of the few studies to assess second-generation (atypical) agents such as clozapine, and there was no evidence of an increase in reactive oxygen species with these newer drugs.

Finally, Post and colleagues[42] administered haloperidol to murine hippocampal HT-22 cells and found a drop in intracellular glutathione and an increase in intracellular peroxides, accompanied by cell death, which was prevented most effectively by vitamin E. The investigators also found evidence that activation of the redox-sensitive nuclear transcription factor NF-κB appeared to be involved in the haloperidol-induced cell death. This suggests that antioxidants, in addition to having a direct role in free radical scavenging, may also reduce oxidative stress by suppressing the activation of transcription factors such as NF-κB.

In addition to the evidence for direct effects of haloperidol, there is also indirect evidence for the increased creation of reactive oxygen species after haloperidol administration, because haloperidol in-

© Adis International Limited. All rights reserved.

hibits complex I of the electron transport chain,[43-45] which could lead to increased free radical generation, especially within mitochondria.

Taken together, the results summarised in this section suggest another mechanism by which antipsychotic medications may be able to cause neuronal damage through an oxidative mechanism, one in which the antipsychotic drugs and their metabolites may be directly neurotoxic or neurotoxic through a mechanism related to the production of free radicals through the mitochondria. It is difficult to understand, however, why such a general toxicity of haloperidol would be expected to result in the specific damage to extrapyramidal structures necessary to result in a movement disorder. One possibility is that haloperidol, by increasing reactive oxygen species globally, may 'use up' antioxidant resources in the brain and that the other antipsychotic-related free radical production mechanisms, which may be more specific to basal ganglia and dopaminergic systems, could then more readily cause damage because of the general reduction in available antioxidant defences.

Consistent with this idea are the findings of Hori et al.,[46] who investigated the genetic association between a functional polymorphism (Ala-9Val) in the human MnSOD gene and both schizophrenia and tardive dyskinesia. Although there was no difference in the allelic or genotypic distribution between patients with schizophrenia and control individuals, there was a significant decrease in the mutant (high-activity) allele in patients with schizophrenia and tardive dyskinesia in comparison with those without tardive dyskinesia. This suggests that the high-activity MnSOD allele may be protective against the development of tardive dyskinesia.

3.2 Oxidative Damage and Antioxidants in Animal Models of Tardive Dyskinesia

Animal models of tardive dyskinesia can be very helpful to determine if there may be free radical–based mechanisms involved in the development of dyskinesia after the administration of antipsychotic medications. Although several animal models of tardive dyskinesia exist, in all cases, antipsychotic medications are given on a long-term basis to an animal and the animal is then observed to determine if motor abnormalities have developed. Antipsychotic medications have typically been delivered in oral form over many days; alternatively, depot, long-acting forms of medications such as fluphenazine or haloperidol decanoate have been injected on a regular basis.

In 1993, Gattaz et al.[47] reported that vitamin E attenuated behavioural hypersensitivity to apomorphine in rats given haloperidol and vitamin E compared with haloperidol alone, suggesting reduced dopamine supersensitivity with vitamin E. Although there are problems with dopamine supersensitivity as a hypothesis of persistent tardive dyskinesia, it is possible that early and reversible forms of antipsychotic-induced dyskinesia, as discussed in section 1, may relate to a dopamine supersensitivity state.[47] These results are also consistent with the possibility that the production of a state of dopamine supersensitivity may itself be associated with increased free radical formation.[47] This finding may also relate to the observation, in clinical studies of vitamin E in tardive dyskinesia, that there is more likely to be a clinical response when the tardive dyskinesia is of relatively recent development.[28] However, it should be pointed out that the Gattaz et al. study[47] did not look directly at any biochemical parameters, so it is not clear if the observed behavioural hypersensitivity reflects dopamine receptor supersensitivity or some other change. Also, it is unclear, if vitamin E were to operate through a mechanism of reduction in supersensitivity, why there would not be a corresponding potential reduction of parkinsonism and possibly psychosis as well; reductions in parkinsonism and psychosis have not been reported in studies of vitamin E in patients with tardive dyskinesia.

Sachdev et al.,[12] in a study of rats treated with fluphenazine decanoate injections every 2 weeks for 12 months, found that selegiline (deprenyl), which has antioxidant and other properties, was associated with reduced vacuous chewing move-

© Adis International Limited. All rights reserved.

ments, mouth tremors and tongue protrusions, but there was no influence of diets high or low in vitamin E. However, the authors noted that the changes in the amount of vitamin E in the diet may not have been sufficient to significantly alter brain vitamin E levels.

Lohr et al.[48] gave fluphenazine decanoate to older rats for 4 months and found not only that a diet high in antioxidants was associated with a reduction in head movements, as measured instrumentally by attached accelerometers, but also that fluphenazine was associated with a significant loss of large cholinergic neurons in the striatum and that the high antioxidant diet prevented this loss. There was also a significant positive correlation between the degree of loss of cholinergic neurons and the degree of movement abnormality.

In summary, the preclinical literature suggests that first-generation antipsychotic agents may be associated with increased free radical activity and behavioural changes, which in some cases appear to be preventable with administration of antioxidants such as vitamin E. It is still unclear whether these preclinical findings are directly relevant to the development of tardive dyskinesia in humans and whether second-generation compounds, such as clozapine, risperidone, ziprasidone, olanzapine and quetiapine, may have a reduced propensity to cause increased free radical activity.

4. Clinical Studies of Oxidative Indices in Antipsychotic Treatment and Tardive Dyskinesia

Just as in the animal studies reviewed in section 3.2, studies can be performed in humans in which measurements of oxidative status can be made in patients given antipsychotic medications. Measurements have been made of transition metals, antioxidants and antioxidant enzymes, as well as of indicators of increased free radical production, such as thiobarbituric acid–reactive substances (TBARS) and conjugated dienes, both of which are indicators of lipid peroxidation.

For many years, both neuropathological and imaging studies have led to observations of increased iron content in the brains of patients treated with antipsychotic medications.[49-52] Studies have also indicated an increase in products of oxidative activity, such as lipid peroxides, in patients treated with antipsychotic medications.[53,54] Pall et al.[53] reported significantly elevated levels of TBARS and conjugated dienes in the CSF of nine non-psychiatric patients receiving phenothiazines, with the highest elevation seen in patients with extrapyramidal signs (but not explicitly tardive dyskinesia). Pai et al.[54] also noted a reduction of glutathione and increased lipid peroxidation in the CSF of patients with acute psychosis who had received haloperidol for 2 weeks, but these changes again were not specifically related to tardive dyskinesia. Apart from the fact that it is not clear from these studies whether such increases in oxidative stress may be related to tardive dyskinesia, it is also not always clear whether these changes are secondary to antipsychotic medications, as opposed to being primary components of psychotic illnesses.

In terms of studies of oxidative activity as related to tardive dyskinesia proper, Lohr et al.[55] found elevated levels of TBARS and conjugated dienes in the CSF of those patients with versus those without tardive dyskinesia, as well as a significant positive correlation between conjugated dienes and scores on the Abnormal Involuntary Movement Scale (AIMS).[56,57] Peet et al.[58] noted a significant positive correlation between severity of dyskinesia and plasma TBARS levels in 14 patients.

McCreadie et al.[59] measured plasma levels of lipid peroxides and vitamin E in patients with and without tardive dyskinesia and in healthy individuals. Although the patients had higher mean lipid peroxide levels and lower mean vitamin E levels than the healthy individuals, there were no significant differences between patients with and without tardive dyskinesia. For lipid peroxide assessment, these investigators used the more specific high-performance liquid chromatography technique rather than the less specific TBARS technique used in other studies.

© Adis International Limited. All rights reserved.

Goff and colleagues[60] measured CSF levels of four substrates of mitochondrial energy metabolism – alanine, aspartate, lactate and pyruvate – and compared these measures in patients with and without tardive dyskinesia. Aspartate levels were significantly elevated in patients with tardive dyskinesia and correlated significantly with the total AIMS score. This finding, consistent with inhibition of complex I of the electron transport chain in the mitochondria, could be associated with increased free radical formation.

A later study from this group,[40] also performed on the CSF of patients with and without tardive dyskinesia, reported evidence of increased excitatory neurotransmission in the brains of patients with tardive dyskinesia, as indicated by significantly higher levels of N-acetylaspartate, N-acetylaspartylglutamate and aspartate. This study also found that the severity of tardive dyskinesia, as measured by the AIMS, correlated positively with markers of excitatory neurotransmission and negatively with CSF SOD activity. Together, these findings confirmed the hypothesis that antipsychotics 'enhance striatal glutamatergic neurotransmission by blocking presynaptic dopamine receptors, which causes neuronal damage as a consequence of oxidative stress'.[40]

Brown and colleagues[61] assayed plasma from patients with schizophrenia, with and without tardive dyskinesia, and from healthy individuals, for vitamin E, vitamin A and TBARS. They found significantly reduced vitamin E, but not vitamin A, levels in the group with tardive dyskinesia compared with the healthy group, but no difference between patients with and without tardive dyskinesia. Using a lipid-corrected assessment of TBARS, the researchers found a significant positive correlation between levels of TBARS and AIMS scores.

Not all studies have found an increase in oxidative stress with antipsychotic treatment. For example, Yao et al.[62] reported a decrease in levels of uric acid (an important water-soluble antioxidant) in plasma following haloperidol discontinuation in patients with schizophrenia, suggesting the possibility that haloperidol may be associated with an increase in uric acid levels.

In terms of the effects of antipsychotics on antioxidant enzymes, the results are inconsistent. Abdalla et al.[63] found no significant differences in erythrocyte SOD and GSH-Px in patients with schizophrenia who were receiving and those who were not receiving antipsychotic medication. Yao and colleagues[64] reported that patients with schizophrenia, when they stopped taking haloperidol for a mean of 40 days, showed increased activity of erythrocyte SOD and GSH-Px, but not catalase.

In summary, although not completely consistent, clinical studies indicate that patients exposed to antipsychotics may demonstrate increased indices of free radical activity, such as increased production of lipid peroxides, both in plasma and CSF. Furthermore, there is some evidence that the amount of peroxidation may relate to the severity of dyskinesia in patients who have tardive dyskinesia. However, the evidence for an association between antipsychotic medications and changes in antioxidant enzymes or water-soluble antioxidants is much less compelling at this point.

5. Clinical Studies of Antioxidant Treatment for Tardive Dyskinesia

The possibility of oxidative processes causing tardive dyskinesia leads to the consideration that antioxidants may be useful in preventing or treating the condition. The hypothesis of free radical damage in tardive dyskinesia suggests that a preventive strategy may be the most useful. However, because oxidative damage may not necessarily be irreversibly neurotoxic in its early stages, the possibility exists that antioxidants may be able to reduce the severity of tardive dyskinesia, especially early in the course of its development. Therefore, an important consideration in antioxidant intervention strategies for tardive dyskinesia concerns timing of the intervention.

Another consideration involves the specific type of intervention to be used. There are several potential strategies here, which relate to the various vulnerabilities to free radical damage in brain

© Adis International Limited. All rights reserved.

regions with elevated catecholamine content described in section 2.2. For example, one could focus on trying to reduce free radical formation by reducing the availability of transition metals, such as by using a chelation strategy. Another strategy could target the antioxidant defence system, whereby antioxidant potential is effectively increased. Here, two factors need to be taken into account. The first is that there are specialised systems for antioxidants depending on whether the primary oxidative process relates to membranes (lipid) or cytosol. The second concerns the fact that antioxidant mechanisms exist in a balance in the organism, so influencing one mechanism may cause changes in another.[26]

So far, the most widely used antioxidant strategy has involved vitamin E, which is the major free radical chain–breaking substance in the body and which is of particular importance in cell membranes. The only consistently reported mechanism of action of vitamin E is that of scavenging free radicals, especially in a lipid environment. Vitamin E is also almost completely free of adverse effects (except for mild stool loosening or diarrhoea) and significant drug interactions when used in dosages at or below 2000 IU/day. Vitamin E may be very useful in cases where lipid peroxidation is important, as the clinical data reviewed in section 4 suggest. Although, theoretically, neuronal membrane systems may be quite vulnerable to attack by free radicals, it is not known if nonmembrane or cytosolic free radical damage may also be important in the pathophysiology of tardive dyskinesia.[26] Vitamin E also may be of limited use if the cells have been destroyed, as the neurons are postmitotic and will not regenerate under most circumstances.

As far as the use of antioxidants as a preventive strategy for tardive dyskinesia is concerned, we are not aware of any studies that have addressed this, although clearly the biochemical considerations outlined in section 2.3 suggest the need for such studies.[65] There is one open-label study[66] that indicated that 600 IU/day of vitamin E may be useful in preventing the development of antipsychotic-induced parkinsonism, but this study did not focus on tardive dyskinesia. This issue may still be of importance to those interested in tardive dyskinesia, however, because there is considerable evidence that the development of parkinsonism may indicate greater risk for the future development of tardive dyskinesia.[3,67,68]

5.1 Vitamin E

So far, most studies of vitamin E in tardive dyskinesia have assessed the efficacy of the vitamin in tardive dyskinesia proper. There have been a substantial number of studies on the use of vitamin E in patients with tardive dyskinesia since our early studies in the late 1980s.[69,70] Studies that were performed with patients in the late 1980s and early 1990s generally indicated that vitamin E was modestly effective in reducing the severity of dyskinesia in tardive dyskinesia.[58,71-84] All of these studies demonstrated a positive effect of vitamin E, with reductions in dyskinesia in the range of 18 to 43%, except the studies of Shriqui et al.,[74] Lam et al.[79] and Dorevitch et al.,[82] which showed no effect. In these latter three studies, it appeared that the tardive dyskinesia was of very long duration in the patients studied, although the exact length of time was frequently unknown. What constitutes clinically meaningful improvement in tardive dyskinesia is not clear, especially since the impact of tardive dyskinesia on the quality of life of individuals, even when the movements are of similar severity, can be very different. In general, many investigators have considered that improvement in the range of 25% or more is probably clinically meaningful.[81]

Two meta-analyses[85,86] of specific studies of the efficacy of vitamin E in patients with tardive dyskinesia demonstrated that vitamin E intervention appeared to be effective in at least a significant subgroup of patients. By the late 1990s, it appeared that in approximately one-third of patients with tardive dyskinesia, treatment with vitamin E in dosages of up to 1600 IU/day could result in some improvement.[85,86] It also seemed that vitamin E was more effective in patients who had had tardive dyskinesia for a shorter (<5 years or so) rather than

© Adis International Limited. All rights reserved.

longer period of time.[85,86] Two studies[83,84] addressed the efficacy of vitamin E over 7 months or more, and both of these studies found a prolonged beneficial effect. However, although most of the studies were double-blind and placebo-controlled, all of these earlier studies involved small numbers of patients.[83-86]

The largest and longest vitamin E study on tardive dyskinesia to date has been the recently completed multisite Veterans Administration Cooperative Study #394 (CS 394).[87] This study of 158 veterans, primarily with schizophrenia, did not demonstrate any significant clinical effect of vitamin E on the severity of tardive dyskinesia as measured by the AIMS over a 12-month period. Both the vitamin E–treated group and the placebo group showed a reduction of tardive dyskinesia severity over the 12 months of the study, but there was no difference in the degree of reduction between the two groups.

We have speculated on the possible reasons for the discrepancy in findings of the CS 394 study[87] in comparison with the earlier smaller studies, most of which demonstrated a positive clinical effect of vitamin E.[88] We divided these reasons into three basic categories related to sampling error, bias and heterogeneity of true effect. In the case of sampling error, it is possible that previous studies were looking at random upward fluctuations that reached a point where a larger study would be warranted, but the results of the larger study would then be expected to regress to the actual value (regression to the mean). Bias is, of course, probably more likely to be a factor in small, tightly controlled studies performed by few investigators, but it is by no means clear that bias cannot be an important component of the findings from large-scale, multisite studies as well. Finally, heterogeneity of true effect could have occurred because of secular trends over time. Because of the length of time and numbers of patients enrolled in the CS 394 study, it was not possible to keep medications as constant as in previous studies, such as the similarly designed study conducted by Adler et al.[84]

In the CS 394 study,[87] a large proportion of patients discontinued anticholinergic medications and switched to second-generation antipsychotics (mainly risperidone). Dosages of antipsychotic medications were considerably lower in the CS 394 study than in many previous studies, reflecting the general practice of reduction in antipsychotic administration in the US during the 1990s. Also, since many patients had been switched to second-generation antipsychotics during the mid-1990s, any patients who had an amelioration of tardive dyskinesia after such a switch would no longer be eligible for entry into CS 394. It was interesting that, although CS 394 was initially designed to look at patients who had had tardive dyskinesia for <5 years, this criterion was dropped because of the lack of availability of such patients in sufficient numbers to meet the needs of the study.

Thus, tardive dyskinesia may have changed over the course of the last decade, and patients who now demonstrate tardive dyskinesia may be those who have experienced irreversible damage or are exceptionally vulnerable to whatever pathophysiological mechanisms are involved. The CS 394 study may have involved a group of patients with a more chronic and refractory form of tardive dyskinesia than in previous studies.

In summary, the role for vitamin E in the treatment of tardive dyskinesia at this time is unclear, but vitamin E does not currently appear to be significantly effective, especially for patients with long-standing tardive dyskinesia. Because of the low toxicity of vitamin E, however, a clinical trial with individual patients may still be worthy of consideration, especially in patients who are in the early stages of development of tardive dyskinesia.

5.2 Other Antioxidants

Selegiline is an irreversible inhibitor of the enzyme MAO-B and has potent antioxidant effects through a number of different mechanisms, including reduced formation of H_2O_2 and increased levels of SOD and CAT. We have already mentioned a rat study in which selegiline was effective in preventing the development of fluphenazine-induced

© Adis International Limited. All rights reserved.

mouth movements (see section 3.2).[12] The only reported study of the use of selegiline in patients with tardive dyskinesia that we are aware of is the study of Goff et al.,[89] which found no effect.

A recent double-blind, placebo-controlled, crossover study[90] of melatonin, which has potent antioxidant properties, reported that a dosage of 10 g/day significantly reduced the severity of tardive dyskinesia, as measured by the AIMS, in 22 patients over a 6-week period. As with selegiline, melatonin has effects on the dopaminergic system apart from its antioxidant properties, so it is not possible to say at this point whether any therapeutic effect of melatonin on tardive dyskinesia is due to its antioxidant potential.

6. Relationship of Oxidative Mechanisms to Other Neurotoxic Mechanisms

At several points in this review, we have reported studies indicating that there may be relationships between oxygen radical neurotoxicity and toxicity produced through other mechanisms in terms of the pathophysiology of tardive dyskinesia. In particular, excitotoxic mechanisms have been reported by some investigators, and it has been speculated that excitotoxic damage may occur through a free radical mechanism, as well as through mechanisms involving problems with mitochondrial energy metabolism (which may also be related to free radical production).[14,40,60,91,92] Because of age-related impairments in the mitochondrial energy system, more free radicals may be formed with increasing age,[27] and this may relate to increased age as a risk factor for tardive dyskinesia. It has also been proposed that excitotoxicity may relate to the observed increase in tardive dyskinesia in patients with substance abuse.[93] Sachdev[9] has suggested that free radical and excitotoxic processes may be responsible for the loss of GABAergic neurons that has been reported in some studies of tardive dyskinesia. In addition, recent evidence suggests that nitric oxide (NO), which can have pro-oxidant or antioxidant properties depending on the circumstances, may also be involved in the pathophysiology of tardive dyskinesia,[94] in that haloperidol may prevent NO-related neuroprotection.

Because of the various interrelationships that may be involved in the pathophysiology of tardive dyskinesia, we considered that it would be helpful to include a diagram indicating the possible mechanisms involved, as well as potential relationships between them (figure 1). It should be kept in mind that this is an illustration of possible relationships, but that the relative importance of these in the pathogenesis of tardive dyskinesia and withdrawal-emergent dyskinesia is yet to be determined.

7. Conclusion

There continues to be scientific evidence supporting the hypothesis that antipsychotic drugs, particularly first-generation (typical) antipsychotic drugs, may cause an increase in free radicals in the brain, and that this increase may relate to the development of tardive dyskinesia. There is some evidence that antioxidant administration may reduce these problems in animals and that at least one antioxidant – vitamin E – may have had some effect on tardive dyskinesia in the early 1990s, although recent studies suggest that there may be little or no effect on tardive dyskinesia currently.

Although vitamin E may have limited use for the treatment of tardive dyskinesia at this time, this issue is still deserving of further research. Antipsychotic drugs, even second-generation (atypical) drugs, can still cause tardive dyskinesia, especially in geriatric patients.[3] In addition, little is known about whether the reduced propensity of second-generation agents to cause tardive dyskinesia may be related to their inability to generate reactive oxygen species or to their potential antioxidant properties. It is possible, for instance, that the relatively decreased dopamine D_2 receptor–blocking ability of second-generation agents in comparison with first-generation agents may contribute to a reduced propensity for tardive dyskinesia, as there may be less secondary increase in dopamine metabolism.

Theoretical considerations and preclinical and clinical studies suggest that antioxidants may be

© Adis International Limited. All rights reserved.

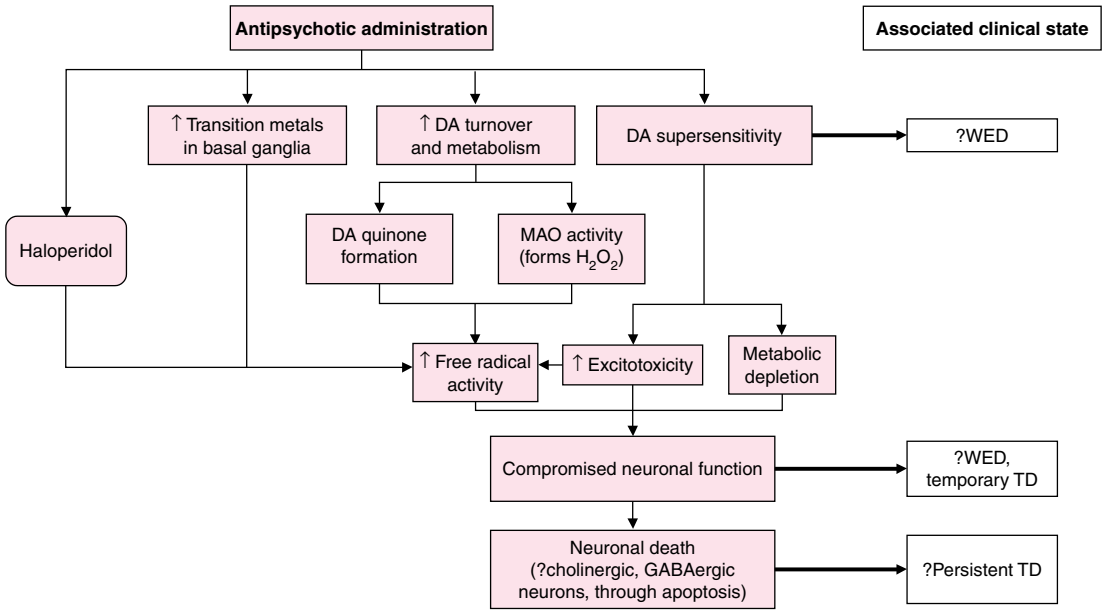

Fig. 1. Potential pathogenetic mechanisms of tardive dyskinesia (TD) in patients receiving antipsychotic therapy. **DA** = dopamine; **GABA** = γ-aminobutyric acid; **MAO** = monoamine oxidase; **WED** = withdrawal-emergent dyskinesia; ↑ indicates increase; **?** indicates uncertain relationship.

most useful as a preventive treatment. Such studies have not so far been undertaken. In patients who have developed tardive dyskinesia, because of the complexity and interactive quality of the antioxidant and other neuroprotective systems, the use of one antioxidant alone, such as vitamin E, may be insufficient. Other antioxidants (such as melatonin[90]), more powerful antioxidants, combinations of antioxidants and antioxidants that can address oxidative damage in multiple systems (such as the amphiphilic vitamin E analogue MDL[95] or propargylamines[96]) may be worth studying as well. Antioxidants that have been reported as potentially useful in the treatment of Alzheimer's disease, such as an extract of gingko biloba, EGb 761[97] or idebenone, a coenzyme Q_{10} analogue,[98] may also be worthy of consideration in studies of tardive dyskinesia. Finally, because of the strong relationships between processes that cause oxidative damage and excitotoxicity,[14,91] the use of neuroprotective or antiexcitotoxic agents, with or without antioxidant treatment, may also be of use. Notably, some of the evidence suggests that mood stabilisers such as valproic acid (sodium valproate), but not lithium,[86] and hormones such as insulin[99] may be of some benefit, likely through neuroprotective, possibly neurotrophic, mechanisms.

Acknowledgements

This work was supported by National Institute of Mental Health Grant R01 57140 and by the Veterans Integrated Service Network (VISN)–22 Mental Illness Research Education and Clinical Center (MIRECC). The authors have provided no information on conflicts of interest directly relevant to the content of this review.

References

1. Lohr JB, Jeste DV. Neuroleptic-induced movement disorders: acute and subacute disorders. In: Cavenar Jr JO, editor. Psychiatry. Philadelphia (PA): Lippincott, 1988: 1-19
2. Glazer WM. Expected incidence of tardive dyskinesia associated with atypical antipsychotics. J Clin Psychiatry 2000; 61 Suppl. 4: 21-6
3. Jeste DV, Caligiuri MP, Paulsen JS, et al. Risk of tardive dyskinesia in older patients: a prospective longitudinal study of 266 outpatients. Arch Gen Psychiatry 1995; 52: 756-65

© Adis International Limited. All rights reserved.

4. Caligiuri MR, Jeste DV, Lacro JP. Antipsychotic-induced movement disorders in the elderly: epidemiology and treatment recommendations. Drugs Aging 2000; 17: 363-84
5. Burt DR, Creese I, Snyder SH. Antischizophrenic drugs: chronic treatment elevates dopamine receptor binding in brain. Science 1977; 196: 326-8
6. Rubinstein M, Muschietti JP, Gershanik O, et al. Adaptive mechanisms of striatal D1 and D2 dopamine receptors in response to a prolonged reserpine treatment in mice. J Pharmacol Exp Ther 1990; 252: 810-6
7. Klawans HL, Rubovits R. An experimental model of tardive dyskinesia. J Neural Transm 1972; 33: 235-46
8. Lohr JB, Jeste DV. Neuroleptic-induced movement disorders: tardive dyskinesia and other tardive syndromes. In: Cavenar Jr JO, editor. Psychiatry. Philadelphia (PA): Lippincott, 1988: 1-17
9. Sachdev PS. The current status of tardive dyskinesia. Aust N Z J Psychiatry 2000; 34: 355-69
10. Cadet JL, Lohr JB. Possible involvement of free radicals in neuroleptic-induced movement disorders: evidence from treatment of tardive dyskinesia with vitamin E. Ann N Y Acad Sci 1989; 570: 176-85
11. Fibiger HC, Lloyd KG. Neurobiological substrates of tardive dyskinesia: the GABA hypothesis. Trends Neurosci 1984; 7: 462-4
12. Sachdev P, Saharov T, Cathcart S. The preventative role of antioxidants (selegiline and vitamin E) in a rat model of tardive dyskinesia. Biol Psychiatry 1999; 46: 1672-81
13. Elkashef AM, Wyatt RJ. Tardive dyskinesia: possible involvement of free radicals and treatment with vitamin E. Schizophr Bull 1999; 25: 731-40
14. Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science 1993; 262: 689-95
15. Hensley K, Floyd RA. Reactive oxygen species and protein oxidation in aging: a look back, a look ahead. Arch Biochem Biophys 2002; 397: 377-83
16. Wickens AP. Ageing and free radical theory. Respir Physiol 2001; 128: 379-91
17. Kesavulu MM, Rao BK, Giri R, et al. Lipid peroxidation and antioxidant enzyme status in type 2 diabetics with coronary heart disease. Diabetes Res Clin Pract 2001; 53: 33-9
18. Dubey RK, Tyurina YY, Tyurin VA, et al. Estrogen and tamoxifen metabolites protect smooth muscle cell membrane phospholipids against peroxidation and inhibit cell growth. Circ Res 1999; 84: 229-39
19. Zima T, Fialova L, Mestek O, et al. Oxidative stress, metabolism of ethanol and alcohol-related diseases. J Biomed Sci 2001; 8: 59-70
20. Mantle D, Preedy VR. Free radicals as mediators of alcohol toxicity. Adverse Drug React Toxicol Rev 1999; 18: 235-52
21. Mercuri F, Quagliaro L, Ceriello A. Oxidative stress evaluation in diabetes. Diabetes Technol Ther 2000; 2: 589-600
22. Turrone P, Seeman MV, Silvestri S. Estrogen receptor activation and tardive dyskinesia. Can J Psychiatry 2000; 45: 288-90
23. Grace AA, Bunney BS, Moore H, et al. Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. Trends Neurosci 1997; 20: 31-7
24. Schultz SK, Miller DD, Arndt S, et al. Withdrawal-emergent dyskinesia in patients with schizophrenia during antipsychotic discontinuation. Biol Psychiatry 1995; 38: 713-9
25. Ahmed S, Chengappa KN, Naidu VR, et al. Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. J Clin Psychiatry 1998; 59: 472-7
26. Halliwell B, Gutteridge JMC. Free radicals in biology and medicine. Oxford: Clarendon Press, 1985
27. Acuna-Castroviejo D, Martin M, Macias M, et al. Melatonin, mitochondria, and cellular bioenergetics. J Pineal Res 2001; 30: 65-74
28. Lohr JB. Oxygen radicals and neuropsychiatric illness: some speculations. Arch Gen Psychiatry 1991; 48: 1097-106
29. Jenner P. Oxidative damage in neurodegenerative disease. Lancet 1994; 344: 796-8
30. Beal MF. Aging, energy, and oxidative stress in neurodegenerative disease. Ann Neurol 1995; 38: 357-66
31. Floyd RA. Antioxidants, oxidative stress, and degenerative neurological disorders. Proc Soc Exp Biol Med 1999; 222: 236-45
32. Bird ED, Collins GH, Dodson MH, et al. The effect of phenothiazine on the manganese concentration in the basal ganglia of sub-human primates. In: Barbeau A, Burnette J-R, editors. Progress in neuro-genetics. Amsterdam: Excerpta Medica, 1967: 600-5
33. Weiner WJ, Nausieda PA, Klawans HL. Effect of chlorpromazine on central nervous system concentrations of manganese, iron, and copper. Life Sci 1977; 20: 1181-6
34. Sagara Y. Induction of reactive oxygen species in neurons by haloperidol. J Neurochem 1998; 71: 1002-12
35. Galili-Mosberg R, Weizman A, Melamed E, et al. Haloperidol-induced neurotoxicity: possible implications for tardive dyskinesia. J Neural Transm 2000; 107: 479-90
36. Murthy JN, Laev H, Karpiak S, et al. Enzymes of oxyradical metabolism after haloperidol treatment in rat [abstract]. Soc Neurosci Abstracts 1989; 15: 139
37. Cadet JL, Perumal AS. Chronic treatment with prolixin causes oxidative stress in rat brain. Biol Psychiatry 1990; 28: 738-40
38. Cohen G, Spina MB. Deprenyl suppresses the oxidant stress associated with increased dopamine turnover. Ann Neurol 1989; 26: 689-90
39. Shivakumar BR, Ravindranath V. Oxidative stress induced by administration of the neuroleptic drug haloperidol is attenuated by higher doses of haloperidol. Brain Res 1992; 595: 256-62
40. Tsai G, Goff D, Chang RW, et al. Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry 1998; 155: 1207-13
41. Behl C, Rupprecht R, Skutella R, et al. Haloperidol-induced cell death: mechanism and protection with vitamin E in vitro. Neuroreport 1995; 7: 360-4
42. Post A, Holsboer F, Behl C. Induction of NF-κB activity during haloperidol-induced oxidative toxicity in clonal hippocampal cells: suppression of NF-κB and neuroprotection by antioxidants. J Neurosci 1998; 18: 8236-46
43. Burkhardt C, Kelly JP, Lim YH, et al. Neuroleptic medications inhibit complex I of the electron transport chain. Ann Neurol 1993; 33: 512-7
44. Prince JA, Hassin MS, Oreland L. Neuroleptic-induced mitochondrial enzyme alterations in the rat brain. J Pharmacol Exp Ther 1997; 280: 261-7
45. Maurer I, Moller HJ. Inhibition of complex I by neuroleptics in normal human brain cortex parallels the extrapyramidal toxicity of neuroleptics. Mol Cell Biochem 1997; 174: 255-9
46. Hori H, Ohmori O, Shinkai T, et al. Manganese superoxide dismutase gene polymorphism and schizophrenia: relation to tardive dyskinesia. Psychopharmacology (Berl) 2000; 23: 170-7
47. Gattaz WF, Emrich A, Behrens S. Vitamin E attenuates the development of haloperidol-induced dopaminergic hypersensitivity in rats: possible implications for tardive dyskinesia. J Neural Transm 1993; 92: 197-201

© Adis International Limited. All rights reserved.

48. Lohr JB, Caligiuri MP, Manley MS, et al. Neuroleptic-induced striatal damage in rats: a study of antioxidant treatment using accelerometric and immunocytochemical methods. Psychopharmacology (Berl) 2000; 148: 171-9
49. Hunter R, Blackwood W, Smith MC, et al. Neuropathological findings in three cases of persistent dyskinesia following phenothiazine medication. J Neurol Sci 1968; 7: 263-73
50. Campbell WG, Raskind MA, Gordon T, et al. Iron pigment in the brain of a man with tardive dyskinesia. Am J Psychiatry 1985; 142: 364-5
51. Bartzokis G, Garber HJ, Marder SR, et al. MRI in tardive dyskinesia: shortened left caudate T2. Biol Psychiatry 1990; 28: 1027-36
52. Casanova MF, Comparini SO, Kim RW, et al. Staining intensity of brain iron in patients with schizophrenia: a postmortem study. J Neuropsychiatry Clin Neurosci 1992; 4: 36-41
53. Pall HS, Williams AC, Blake DR, et al. Evidence of enhanced lipid peroxidation in the cerebrospinal fluid of patients taking phenothiazines. Lancet 1987; II: 596-9
54. Pai BN, Janakiramaiah N, Gangadhar BN, et al. Depletion of glutathione and enhanced lipid peroxidation in the CSF of acute psychotics following haloperidol administration. Biol Psychiatry 1994; 36: 489-91
55. Lohr JB, Kuczenski R, Bracha HS, et al. Increased indices of free radical activity in the cerebrospinal fluid of patients with tardive dyskinesia. Biol Psychiatry 1990; 28: 535-9
56. National Institute of Mental Health. Abnormal involuntary movement scale. In: Guy W, editor. Early clinical evaluation unit assessment manual. Rockville (MD): US Department of Health and Human Services, 1976: 534-7
57. Schooler NR, Kane JM. Research diagnosis for tardive dyskinesia [letter]. Arch Gen Psychiatry 1982; 39: 486-7
58. 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
59. McCreadie RG, MacDonald E, Wiles D, et al. The Nithsdale schizophrenia surveys. XIV: plasma lipid peroxide and serum vitamin E levels in patients with and without tardive dyskinesia, and in normal subjects. Br J Psychiatry 1995; 167: 610-7
60. Goff DC, Tsai G, Beal MF, et al. Tardive dyskinesia and substrates of energy metabolism in CSF. Am J Psychiatry 1995; 152: 1730-6
61. Brown K, Reid A, White T, et al. Vitamin E, lipids, and lipid peroxidation products in tardive dyskinesia. Biol Psychiatry 1998; 43: 863-7
62. Yao JK, Reddy R, van Kammen DP. Reduced level of plasma antioxidant uric acid in schizophrenia. Psychiatr Res 1998; 80: 29-39
63. Abdalla DSP, Manteiro HP, Olivera JAC, et al. Activities of superoxide dismutase and glutathione peroxidase in schizophrenic and manic depressive patients. Clin Chem 1986; 32: 805-7
64. Yao JK, Reddy R, McElhinny LG, et al. Effects of haloperidol on antioxidant defense system enzymes in schizophrenia. J Psychiatr Res 1998; 32: 385-91
65. Gattaz WF. Does vitamin E prevent tardive dyskinesia? Biol Psychiatry 1995; 37: 895-7
66. Dorfman-Etrog P, Hermesh H, Prilipko L, et al. The effect of vitamin E addition to acute neuroleptic treatment on the emergence of extrapyramidal side effects in schizophrenic patients: an open label study. Eur Neuropsychopharmacol 1999; 9: 475-7
67. Crane GE. Pseudoparkinsonism and tardive dyskinesia. Arch Neurol 1972; 27: 426-30
68. Caligiuri MP, Lohr JB, Bracha HS, et al. Clinical and instrumental assessment of neuroleptic-induced parkinsonism in patients with tardive dyskinesia. Biol Psychiatry 1991; 29: 139-48
69. Lohr JB, Cadet JL, Lohr MA, et al. Alpha-tocopherol in tardive dyskinesia: a preliminary study. Lancet 1987; I: 913-4
70. Lohr JB, Cadet JL, Lohr MA, et al. Vitamin E in the treatment of tardive dyskinesia: the possible involvement of free radical mechanisms. Schizophr Bull 1988; 14: 291-6
71. Elkashef AM, Ruskin PE, Bacher N, et al. Vitamin E in the treatment of tardive dyskinesia. Am J Psychiatry 1990; 147: 505-6
72. Schmidt M, Meister P, Baumann P. Treatment of tardive dyskinesias with vitamin E. Eur Psychiatry 1991; 6: 201-7
73. Egan MF, Hyde T, Albers G, et al. Treatment of tardive dyskinesia with vitamin E. Am J Psychiatry 1992; 149: 773-7
74. Shriqui CL, Bradwejn J, Annable L, et al. Vitamin E in the treatment of tardive dyskinesia: a double-blind placebo-controlled study. Am J Psychiatry 1992; 149: 391-3
75. Spivak B, Schwartz B, Radwan M, et al. Alpha-tocopherol treatment for tardive dyskinesia. J Nerv Ment Dis 1992; 180: 400-1
76. Junker D, Steigleider P, Gattaz WF. Alpha-tocopherol in the treatment of tardive dyskinesia. Clin Neuropharmacol 1992; 15 (Suppl. 1, Pt b): 639B
77. Akhtar S, Jajor TR, Kumar S. Vitamin E in the treatment of tardive dyskinesia. J Postgrad Med 1993; 39: 124-6
78. Adler L, Peselow E, Rotrosen J, et al. Vitamin E treatment of tardive dyskinesia. Am J Psychiatry 1993; 150: 1405-7
79. Lam LCW, Chiu HFK, Hung SF. Vitamin E in the treatment of tardive dyskinesia: a replication study. J Nerv Ment Dis 1994; 182: 113-4
80. Dabiri LM, Pasta D, Darby JK, et al. Effectiveness of vitamin E for treatment of long-term tardive dyskinesia. Am J Psychiatry 1994; 151: 925-6
81. Lohr JB, Caligiuri MP. A double-blind placebo controlled study of vitamin E treatment of tardive dyskinesia. J Clin Psychiatry 1996; 57: 167-73
82. Dorevitch A, Kalian M, Shlafman M, et al. Treatment of long-term tardive dyskinesia with vitamin E. Biol Psychiatry 1997; 41: 114-6
83. Sajjad SHA. Vitamin E in the treatment of tardive dyskinesia: a preliminary study over 7 months at different doses. Int Clin Psychopharmacol 1998; 13: 147-55
84. Adler LA, Edson R, Lavori P, et al. Long-term treatment effects of vitamin E for tardive dyskinesia. Biol Psychiatry 1998; 43: 868-72
85. Barak Y, Swartz M, Shamir E, et al. Vitamin E (α-tocopherol) in the treatment of tardive dyskinesia: a statistical meta-analysis. Ann Clin Psychiatry 1998; 10: 101-5
86. Soares KVS, McGrath JJ. The treatment of tardive dyskinesia: a systematic review and meta-analysis. Schiz Res 1999; 39: 1-16
87. Adler LA, Rotrosen J, Edson R, et al. Vitamin E treatment for tardive dyskinesia. Arch Gen Psychiatry 1999; 56: 836-41
88. Lohr JB, Lavori P. Whither vitamin E and tardive dyskinesia? Biol Psychiatry 1998; 43: 861-2
89. Goff DC, Renshaw PF, Sarld-Segal O, et al. A placebo-controlled trial of selegiline (L-deprenyl) in the treatment of tardive dyskinesia. Biol Psychiatry 1993; 33: 700-6
90. Shamir E, Barak Y, Shalman I, et al. Melatonin treatment for tardive dyskinesia: a double-blind, placebo-controlled, crossover study. Arch Gen Psychiatry 2001; 58: 1049-52

© Adis International Limited. All rights reserved.

91. Andreassen OA, Jorgensen HA. Neurotoxicity associated with neuroleptic-induced oral dyskinesias in rats: implications for tardive dyskinesia? Prog Neurobiol 2000; 61: 525-41
92. Zeevalk GD, Bernard LP, Nicklas WJ. Oxidative stress during energy impairment in mesencephalic cultures is not a downstream consequence of a secondary excitotoxicity. Neuroscience 2000; 96: 309-16
93. Bailey LG, Maxwell S, Brandabur MM. Substance abuse as a risk factor for tardive dyskinesia: a retrospective analysis of 1027 patients. Psychopharmacol Bull 1997; 33: 177-81
94. Harvey BH, Bester A. Withdrawal-associated changes in peripheral nitrogen oxides and striatal cyclic GMP after chronic haloperidol treatment. Behav Brain Res 2000; 111: 203-11
95. Bolkenius FN, Verne-Mismer J, Wagner J, et al. Amphiphilic α-tocopherol analogues as inhibitors of brain lipid peroxidation. Eur J Pharmacol 1996; 298: 37-43
96. Kitani K, Minami C, Yamamoto T, et al. Do antioxidant strategies work against aging and age-associated disorders? Propargylamines: a possible antioxidant strategy. Ann N Y Acad Sci 2001; 928: 248-60
97. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of ginkgo biloba for dementia: the North American EGb Study Group. JAMA 1997; 278: 1327-32
98. Gutzmann H, Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. J Neural Transm Suppl 1998; 54: 301-10
99. McGrath JJ, Soares KV. Miscellaneous treatments for neuroleptic-induced tardive dyskinesia. The Cochrane Database of Systematic Reviews. Available in The Cochrane Library [database on disk and CD ROM]. Updated quarterly. The Cochrane Collaboration; issue 4. Oxford: Oxford Update Software, 2000

Correspondence and offprints: Dr *James B. Lohr*, Psychiatry Service V-116A, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, USA.
E-mail: jlohr@ucsd.edu

© Adis International Limited. All rights reserved.