Appendix 3

Modification of antipsychotic medication as a treatment for tardive dyskinesia (level of evidence 1-)

Cochrane Review(1)

Of the five studies included in the Cochrane review(1), two (2, 3) compared the effect on TD of antipsychotic dose reduction versus continued treatment at a fixed dose. Cookson compared flupenthixol decanoate dose reduction by 50% versus maintenance of a stable dose for 44 weeks in 18 people (of whom only nine had established TD), while Kane compared antipsychotic dose reduction by 1.25-5 mg every two weeks to a maintenance dose of 12.5-50 mg for 52 weeks in 8 people. Meta-analysis of the results from these two studies showed that dose reduction may be associated with a clinically significant reduction in TD severity (RR 0.38 CI 0.1 to 1.0). Due to the very limited number of participants in these two studies, replication studies are needed using antipsychotics doses typical of current practise to determine if dose reduction leads to improved TD outcomes while maintaining efficacy.

The other three RCTs included in the Cochrane review compared the effect on TD of different antipsychotic medications (4-6). Glazer's study included eighteen individuals with long-term exposure to antipsychotic medication who developed TD while having their existing medication tapered and withdrawn. These individuals were randomized to molindone or haloperidol to compare the ability of these two antipsychotic medications to mask withdrawal-emergent TD symptoms. Two dosages of haloperidol and molindone were used for each week of this two-week study. During the first week, molindone 75 mg was compared with haloperidol 19.3 mg; during the second week, dosages were increased to 200% of the pre-study antipsychotic dose. There was no significant difference between haloperidol and molindone on the AIMS score after the first week of treatment. After the second week of treatment using the higher masking dosages, a significant result in favour of haloperidol was found on the AIMS score, indeed the haloperidol-treated group's AIMS score decreased by 53.2% of the baseline as compared to 23.4% in the molindone-treated group ($P<0.0001$).

Emsley et al (4) conducted a single-blind randomized trail comparing the effect on TD of quetiapine (400 mg/day) versus haloperidol (10 mg/day) in a 50-week study of 47 people. All patients had TD from previous exposure to antipsychotics and they were tapered from previous psychotropic medications over 2-week period. Tardive dyskinesia was assessed using the Clinical Global Impression (CGI)-Dyskinesia score, evaluating the proportion of participants with a greater than or equal to 50% reduction in score. The response rate for quetiapine and haloperidol respectively were 64% and 37% at 6 months and 55% and 28% at 12 months, with the CGI-Dyskinesia declining significantly more with quetiapine than haloperidol (p=0.002).

Kazamatsuri et al (7) compared the effect of haloperidol (maximum 16 mg/day) to thiopropazate (maximum 80 mg/day) on tardive dyskinesia in a study of four weeks duration in 20 people. No difference was found between treatments.

Vitamin E for tardive dyskinesia (level of evidence 1-)

Vitamin E (tocopherol) is a lipid-soluble antioxidant. It is a free radical scavenger, which has been suggested as a possible treatment for tardive dyskinesia (TD) (8).

A Cochrane review (last updated in 2011) was performed to determine the effects of vitamin E for people with schizophrenia or other chronic mental illnesses who developed antipsychotic-induced TD (9). Randomized controlled trials of individuals with TD who were randomly allocated to vitamin E or placebo were included in the review. Eleven studies met inclusion criteria, with 427 participants (10-14). Most participants in studies were males with schizophrenia, with an average age of 50 years. Trials were published between 1990 and 1999. Risk of bias was low in 8 trials (Class II) and high in three trials (Class III). Duration of treatment ranged from 2 weeks to 12 months (majority of studies 10-12 months). The dose of vitamin E ranged from 600 IU-1600 IU, with most studies using higher doses (5 studies 1600 IU, 5 studies 1200 IU). In all studies, vitamin E was added to a “stable” dose of antipsychotic medication. All except two studies were parallel group studies, with the remainder employing a cross-over design. The primary outcome in all studies was the change in AIMS score. For the Cochrane review, clinically significant improvement in tardive dyskinesia was defined as a 50% reduction

in symptoms of TD on any scale.

For the outcome of “clinically significant improvement in tardive dyskinesia”, there was no difference between vitamin E and placebo, with data from 6 trials and 256 people demonstrating a risk ratio of 0.95, 95%CI 0.89-1.02. For the outcome of “any improvement in TD symptoms”, data from 7 trials and 311 people demonstrated a risk ratio of 0.86, 95% CI 0.75-1.00, suggesting a minor improvement in TD or no improvement. People allocated to placebo showed more deterioration of their TD symptoms compared with those allocated to vitamin E, with data from 5 trials and 98 people demonstrating a risk ratio of 0.38, 95% CI 0.16-0.90. There was no difference in the incidence of adverse effects between vitamin E and placebo-treated individuals, with a risk ratio of 1.29, CI 0.51-3.24. There is evidence that suggests high-dose, long-term vitamin E supplementation (above 400 IU per day) may be associated with an increased risk of mortality (15).

Recommendation (Grade B): Vitamin E use does not lead to clinically important improvement of tardive dyskinesia once it is established, but may protect against deterioration of TD.

Benzodiazepines for neuroleptic-induced tardive dyskinesia (level of evidence 1-)
A Cochrane review (last updated in 2006 (16)) has evaluated the effects of benzodiazepines for antipsychotic-induced tardive dyskinesia in people with schizophrenia, schizoaffective disorder or other chronic mental illnesses. This review included randomized controlled trials evaluating the effect of any benzodiazepine drug, at any dose or means of administration, compared with either placebo or no intervention for the treatment of tardive dyskinesia. Only three studies (Class II), randomising a total of 56 people, met the inclusion criteria (17-19))

All studies used benzodiazepines as an adjunct to the standard treatment already being received by the patients. Weber et al compared diazepam (6-25 mg/day, mean 12

mg/day) with no additional treatment to standard care. Csernansky and collegues (17) compared diazepam (mean stable dose, 48.3 and 19.4 mg) with alprazolam (mean stable dose 7.2 and 1.8 mg) and placebo. Xiang (20) compared clonazepam (4-6 mg/day) with placebo. The duration of treatment ranged from 6 weeks to 24 weeks. Only Weber et al (18) provided details of the age of the participants, the average age being approximately 57 years. The outcomes assessed included change in tardive dyskinesia severity as measured on the AIMS scale, a Chinese version of the AIMS named the Abnormal Involuntary Movement Scale - AMS (Reference not quotable) (19), and the Gerlach Dyskinesia Scale - GDS (17). Only Weber et al. reported mental state changes using the Brief Psychiatric Rating Scale (BPRS) and loss to follow up. Adverse effects were not reported in any of the studies.

Both (17) and (18) found no difference between groups for the outcome 'clinically important improvement', arbitrarily defined by the authors as a 50% improvement in any scale for TD (n=30, 2 RCTs, RR 1.08 CI 0.57 to 2.05). They found no difference in the outcome 'not improved to any extent' (RR 1.19 CI 0.3 to 5.3), 'deterioration' (RR 1.85 CI 0.3 to 10.1), or in 'average change in tardive dyskinesia score' as per AIMS (n=13, WMD -4.77, CI -10.81 to 1.27) or GDS scale (n=17, WMD 1.03, CI -0.47 to 2.53). Xiang et al. (20) did not measure the mean change in the AMS scale but found a statistically significant difference in endpoint scores using the AMS scale, favouring those receiving benzodiazepines (n=24, WMD -3.22 CI -4.63 to -1.81). Bhoopathi and colleagues commented that one cannot be entirely sure that the AMS is a valid scale, or what the decline of four points means in terms of clinical signs and symptoms (16). We also included 1 class II from the AAN review which evaluated the effect of 4.5 mg of clonazepam on 19 patients with tardive dyskinesia which showed 26% improvement after 12 weeks (21).

Recommendation (Grade B)

Currently, there is little evidence to support that benzodiazepines have any effect in reducing tardive dyskinesia. Moreover, given evidence of acute and long-term harm (sedation, worsening of cognitive functions, tolerance, dependence and risk of falls

especially in elderly people) from benzodiazepine use in patients with mental health disorders, the routine use of benzodiazepines is discouraged.

Gamma-aminobutyric acid (GABA) agonists for antipsychotic-induced tardive dyskinesia (level of evidence 1-)

A Cochrane review (22) was performed to determine the clinical effects of non-benzodiazepine GABA agonist drugs (baclofen, gamma-vinyl-GABA, gamma-acetylenic-GABA, progabide, muscimol, sodium valproate, and tetrahydroisoxazolopyridine) for people with schizophrenia or other chronic mental illnesses who developed antipsychotic-induced tardive dyskinesia. Controlled trials in which participants were randomly allocated to either a GABA agonist or placebo/no intervention were included in the review, with eight trials identified for inclusion. These eight trials included four trials of baclofen, one trial of progabide, two trials of sodium valproate, and one trial of tetrahydroisoxazolopyridine. The eight included trials were all short in duration, with no study exceeding six weeks. Five of the eight studies used a crossover design. A total of 185 people were included in the eight studies.

Of the four studies evaluating baclofen, one was Class II and three were Class III. The dosage of baclofen ranged from 20 to 120 mg per day. There was no difference between baclofen and placebo in any of the efficacy outcomes for tardive dyskinesia. For the outcome ‘not improved to a clinically important extent’, the risk ratio was 0.78 (0.46, 1.31) based on one study including 33 participants. For the outcome ‘not any improvement’, the risk ratio was 1.01 (0.37, 2.74) based on two studies including 43 participants. For the outcome ‘deterioration of symptoms’, the risk ratio was 1.08 (0.17, 6.78) based on three studies including 61 participants.

The one trial of progabide was Class III, and studied doses of 20, 30 or 45 mg/kg/day in a total of 13 participants. There was no difference between progabide and placebo in any of the efficacy outcomes for tardive dyskinesia. For the outcome ‘not improved to a clinical important extent’, the risk ratio was 0.68 (0.36, 1.25). For the outcome ‘not any improvement’, the risk ratio was 1.09 (0.05, 21.67).

The two trials of sodium valproate were rated Class II and Class III. The dose of sodium valproate was 900 mg per day in one study and 1500 mg per day in the other study. There was no difference between sodium valproate and placebo in any of the efficacy outcomes for tardive dyskinesia. For the outcome 'not improved to a clinically important extent', the risk ratio was 0.94 (0.80, 1.11), based on one study including 62 participants. For the outcome 'not any improvement', the risk ratio was 0.72 (0.35, 1.46), based on two studies including 94 participants. For the outcome 'deterioration of symptoms', the risk ratio was 2.64 (0.58, 12.06), based on one study including 62 participants.

One study of tetrahydroisoxazolopyridine was rated Class III, and included 2 participants, one taking a dose of 120 mg/day and the other taking 60 mg/day. There was no difference beween tetrahydroisoxazolopyridine and placebo in the outcome, not any improvement, with a risk ratio of 0.33 (0.03, 4.19).

We identified and added one more Class II study comparing baclofen (30-90 mg per day) to placebo. No difference between groups was detected(23).

Recommendation (Grade B): Due to evidence of no effect and to the risk of side effects (ataxia, sedation), non-benzodiazepine GABA agonists (baclofen, gamma-vinyl-GABA, gamma-acetylenic-GABA, progabide, muscimol, sodium valproate, and tetrahydroisoxazolopyridine, piracetam, levetiracetam) are not recommended for the treatment of tardive dyskinesia.

Cholinergic medication for antipsychotic-induced tardive dyskinesia (level of evidence 1-)

A Cochrane review (24) was performed to determine the effect of cholinergic drugs (arecoline, choline, deanol, lecithin, meclofenoxate, physostigmine, RS86, tacrine, metoxytacrine, galantamine, ipidacrine, donepezil, rivastigmine, eptastigmine, metrifonate, xanomeline, cevimeline) for the treatment of antipsychotic-induced tardive dyskinesia in people with schizophrenia or other chronic mental illness. Controlled trials

in which participants were randomized to either a cholinergic agent or placebo or no intervention were included, with eleven studies identified for inclusion. These eleven studies included four studies of lecithin (25-28), six studies of deanol (29 , 30 , 31 , 32 , 33 , 34)), and one study of meclofenoxate (35). We identified two additional studies of galatamine and donepezil published after the Cochrane review was completed (36, 37), which we have added to this summary.

Of the studies of lecithin, deanol and meclofenoxate, most studies were short term, lasting less than six weeks. People involved in the trials were mostly long-term inpatients of middle age with schizophrenia. The number of people in the studies ranged from five to sixty.

The four studies of lecithin used doses from 20 to 35 grams per day. All studies were rated Class II. There was no difference between lecithin and placebo in any of the efficacy outcomes for tardive dyskinesia. For the outcome ‘no clinically important improvement’, defined as a 50% or more change on any validated scale for tardive dyskinesia, the risk ratio was 0.71 (0.31, 1.66), based on one study including six participants. For the outcome ‘not any improvement’, the risk ratio was 0.87 (0.63, 1.21) as assessed by rater at less than six weeks based on two trials of 36 participants, and was 0.92 (0.62, 1.36) as assessed by self-report at less than six weeks, based on one trial of 30 participants. The average end-point score on the AIMS was no different between lecithin and placebo treated participants, with a mean difference of -0.10 (-1.04, 0.84) at more than six weeks in one trial of 14 participants, and a mean difference of -1.07 (-2.21, 0.07) at less than six weeks in one trial of six participants.

The six studies of deanol used doses from 1 to 2 grams per day. Two studies were rated Class II and four studies were rated class III. There was no difference between deanol and placebo in any of the efficacy outcomes for tardive dyskinesia. For the outcome ‘no clinically important improvement’, defined as a 50% or more change on any validated scale for tardive dyskinesia, the risk ratio was 0.84 (0.39, 1.81), based on two studies including 11 participants. For the outcome ‘not any improvement’, as

assessed by rater, the risk ratio was 0.81 (0.26, 2.57) at more than six weeks based on two studies of 11 participants, and was 0.83 (0.58, 1.18) at less than six weeks based on three studies of 63 participants. The average end-point score on the AIMS was not different between deanol and placebo treated participants, with a mean difference of 1.42 (-0.29, 3.13) based on one study of six participants.

The study of meclofenoxate used a dose of 900 mg per day and was rated Class II. There was no difference between meclofenoxate and placebo in any of the efficacy outcomes for tardive dyskinesia. For the outcome ‘not any improvement’, the risk ratio was 0.84 (0.55, 1.27), based on one study of 60 participants. The average end-point score on the AIMS was not different between meclofenoxate and placebo treated participants, with a mean difference of -0.19 (-0.58, 0.20) based on one study of sixty participants.

We identified one Class II study (36) of galantamine for the treatment of tardive dyskinesia. This trial included 35 male patients with schizophrenia, randomly assigned to receive 8 to 24 mg of galantamine or placebo for two 12-week phases separated by a 4-week washout period. For the primary outcome (total AIMS score at endpoint), there was no difference between galantamine and placebo. Simpson-Angus scale ratings of parkinsonism were significantly higher with galantamine than placebo.
We identified one Class III study (37) for donepezil for the treatment of tardive dyskinesia. This trial included ten patients and was designed as a crossover study comparing donepezil 5 or 10 mg with placebo. No difference was found on the AIMS with donepezil at a dose of 5 or 10 mg compared with placebo treatment.

Recommendation (Grade B): Due to evidence of no effect, cholinergic medications (arecoline, choline, deanol, lecithin, meclofenoxate, physostigmine, RS86, tacrine, metoxytacrine, galantamine, ipidacrine, donepezil, rivastigmine, eptastigmine, metrifonate, xanomeline, cevimeline) are not recommended for the treatment of tardive dyskinesia.

Miscellaneous treatments for antipsychotic induced tardive dyskinesia (level of evidence 1-)

A Cochrane review(38) evaluated a number of medications, which do not fit into any of the other Cochrane review treatment categories, for their effect on TD. This review included 31 randomized controlled trials of 24 interventions in 1278 adult participants with chronic psychiatric disorders, mainly schizophrenia. The majority of studies were of short duration (three to six weeks) with sample sizes ranging from 10 to 157 participants. Most studies were published more than 20 years ago and the risk of bias was unclear for many studies. For the primary outcome, no clinically important improvement in TD symptoms, the review reported low to very low evidence of a benefit for buspirone, dehydrogenated ergot alkaloids, hypnosis or relaxation, pemoline, promethazine, insulin, branched chain amino acids, and isocarboxazid. There was low to very low evidence of no difference between intervention and placebo or no treatment for ceruletine, phenylalanine, piracetam melatonin, lithium, ritanserin, selegiline, oestrogen, and gamma-linolenic acid. There was moderate quality evidence of benefit for extract of ginko biloba compared to placebo, however due to small sample size, the effect is uncertain. One of two studies of levetiracetam found a benefit in favour of levetiracetam compared to placebo on the AIMS scale, but neither study reported on the primary outcome for the review.

We found two further studies investigating other miscellaneous treatments for TD. Two studies (1 class II and 1 class III studies) evaluating the effect of diltiazem on tardive dyskinesia (39, 40) did not show any significant improvement on TD symptoms.

Recommendation (Grade B): There is insufficient evidence to recommend the use of ginko biloba, levetiracetam, buspirone, dehydrogenated ergot alkaloids, hypnosis or relaxation, pemoline, promethazine, insulin, branched chain amino acids, and isocarboxazid for the treatment of tardive dyskinesia. Due to evidence of no effect, ceruletine, phenylalanine, piracetam, melatonin, lithium, ritanserin, selegiline,

oestrogen, gamma-linolenic acid and diltiazem are not recommended for the treatment of tardive dyskinesia.

Reserpine and alpha methyldopa (level of evidence 1-)

There is one class III study of 30 inpatients with psychosis and TD, comparing reserpine, alpha methyldopa and placebo treatment (41). Participants received up to 1500 mg of alpha methyldopa or up to 1.5 mg of reserpine, or placebo, for a period of two weeks. Treatment with either drug resulted in significant improvement in dyskinesia ratings compared with placebo. Side effects of the medication were not reported.

Recommendation (Grade B): Given the very limited and low quality evidence for alpha methyldopa and reserpine as treatments for TD, use of other dopamine depletors (valbenazine and deutetrabenazine) is advised.

Deep Brain Stimulation in patients with medication-induced tardive dyskinesia and/or dystonia (Level 2+)

Multiple single case reports and open-label small case series have suggested that deep brain stimulation (DBS) of the internal part of the globus pallidus (GPi-DBS) could be highly effective in the treatment of patients with medically intractable TD(42).
Recently the French Stimulation for Tardive Dyskinesia (STARDYS) Study demonstrated in a short-term, double-blind evaluation of the efficacy of bilateral GPi-DBS in 10 patients with severe TD. At 6 months after surgery, the ESRS score decreased compared with baseline by more than 40% (mean improvement, 61%; range, 44%-75%) in these 10 patients included (43).
To confirm the efficacy and the safety of GPi-DBS for TD, the same study group continued the previous study including 10 additional patients and by extending the follow-up time. They included in the final analysis 19 patients with severe pharmacoresistant TD and assessed the efficacy of GPi-DBS at baseline, 6 and 12 months post surgery. Fourteen patients had a long follow-up of 6–11 years. The assessment included motor functions (ESRS, and AIMS) and cognitive and a

psychiatric symptoms. Compared to baseline, all patients had a decrease of the ESRS score which was 40% at 6 months and 58% at 12 months follow-up. AIMS improved of 50% at 6 months follow-up. In the 14 patients with long follow-up, the improvement was maintained, with a 60% decrease in the total ESRS score and a 63% in the total AIMS score in comparison to baseline scores (44).

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