TOURETTE SYNDROME and PHARMACOTHERAPY

The mechanisms of Tourette syndrome remain poorly understood, and pharmacotherapy treatments are further complicated by the challenges arising from the fact that the genetics, neurophysiology, and neuropathology of Tourette syndrome are still largely unknown. Within Tourette syndrome pharmacotherapy falls into four broad categories being alpha agonists, dopamine depleters, anti-psychotics, and topiramate. Other pharmacological approaches include novel, experimental, and complimentary medicines, such as traditional Chinese therapies and cannabinoids. Pharmacotherapy primarily focuses on the treatment of tics, which are brief, intermittent movements (motor) or sounds (phonic), often heralded by a premonitory urge. Pharmacotherapy is normally considered where a rapid effect is sought, and where tics cause impairment, interfere with daily life, cause emotional distress, or physical injury (Martino, 2020). Males tend to be more affected by tics, than females (Cothros, Medina, & Pringsheim, 2020). There remains an elusive balance within pharmacotherapy between a medicine's efficacy and its side effects, and as such all pharmacotherapy in Tourette syndrome requires drug safety monitoring and re-evaluation over time.

Alpha Agonists

Alpha agonists include guanfacine and clonidine. When ADHD is present in Tourette syndrome the case is strengthened for the use of alpha agonists. In North America alpha agonists are considered first-line pharmacotherapy in children with Tourette syndrome (Roessner, et al., 2011). The main adverse effects associated with alpha agonists include dry mouth, irritability, headache, stomachache, hypotension, bradycardia (where low heart rate causes fatigue, weakness, dizziness, sweating, and at very low rates, fainting), and sedation. Improvements may take up to twelve weeks to be evident. Because of the modest efficacy evident within alpha

agonist use, it is suggested that these medications may be helpful in patients with mild tics that are troublesome enough to require pharmacologic therapy (Jankovic, 2020).

Antipsychotics

In tics which are refractory to other measures, the case is strong for the use of antipsychotic medication. Findings from dopaminergic presynaptic and postsynaptic imaging studies support the pivotal role of dopamine in pharmacotherapy. Dopamine blocking agents are considered the most effective and potent pharmacotherapy for tics (Pringsheim, et al., 2019). A limitation of these medications are side effects which include adverse metabolic effects (elevated blood levels of lactose that can be associated with muscle damage, neuropathy, pancreatitis, liver failure, and fatty growths), hyperprolactinemia (where excess prolactin affects menstrual cycles, or may cause erectile dysfunction or infertility), weight gain, drug induced movement disorders, and QT prolongation (a heart rhythm condition that can cause fast, chaotic heartbeats, and may trigger a sudden fainting spell or seizure).

Antipsychotics, also known as neuroleptics, include haloperidol, pimozide, fluphenazine, risperidone, ziprasidone, aripiprazole, tiapride, and sulpiride. Most are generally dopamine receptor blocking drugs. The use of first-generation antipsychotics haloperidol, pimozide, and fluphenazine has decreased over time due to the availability of medications with more favourable side effect profiles. Although Zelnik (2020), reported haloperidol and pimozide as the most reliable antipsychotic medication in terms of treatment response. Risperidone and ziprasidone emerged as part of the second generation of antipsychotics. Of the third-generation antipsychotics of tiapride, aripiprazole, and sulpiride, aripiprazole appears to be a first choice. Aripiprazole's potential role in treating co-morbidities and its FDA approval has supported its

growing use (Cothros, et al., 2020), however there have been reports of tardive dyskinesia (uncontrolled stiff, jerky movements of face and body) as an adverse effect (Jankovic, 2020).

Antiepileptic Drugs (Topiramate)

Antiepileptic drugs include topiramate and botulinum. There is currently weak evidence supporting topiramate, with only one double-blind placebo-controlled cross over trial finding it is possibly more likely than placebo to reduce tic severity (Jankovic et al., 2010). No studies have emerged that support their use as a mainstay treatment. As with topiramate, only one randomized control trial has taken place on botulinum toxin, which concluded botulinum is probably more likely than placebo to reduce tic severity (Marras, et al., 2001). Botulinum appears to be well tolerated for motor tics involving the face and neck muscles, and appears to be highly effective in the treatment of simple motor tics. Muscle weakness can occur but is rarely disabling and is always transient (Jankovic, 2020).

Dopamine Depleters

Dopamine depleters include tetrabenazine, deuterobenzene, and valbenazine. These medications are often associated with undesirable adverse effects such as metabolic effects and tardive dyskinesia (Jankovic, 2020). While results of early studies on deuterobenzene and valbenazine remain promising, randomised controlled trials on these medications are needed.

Complementary and Alternative Medicine

There is little research on the efficacy and safety of complementary or alternative therapies in Tourette syndrome, and the exact prevalence of use is unknown. Concerns around the potential side effects of pharmacological treatments, or difficulty in accessing interventions for tics has supported the consideration of complementary and alternative medicine, which are

often perceived as safe or natural. In one study of 110 participants, the most commonly used therapies included stress management, herbal medicine, homeopathy, and meditation, with the majority of users reporting benefits greater than medication. Herbal medicines included lavender oil, CBDE oil, peppermint oil, evening primrose, and ginseng. The majority (46%) reported getting their information from TV/internet. Caregivers who earned more than $100,000.00 per annum were less likely to use these alternatives. Overall, 46% reported these alternatives helping more than pharmacotherapy, with their primary drive being to find a nonpharmacologic treatment that had no side effects (Patel, et al., 2020). McCann and Newell (2006) reported 62% of patients seen through outpatient clinics reporting some use of a form of complementary or alternative therapy.

Traditional Chinese medicine has been used in many countries in the treatment of psychiatric disorders. The findings on the efficacy and safety of traditional Chinese medicines are mixed (Qi, et al., 2020). Other studies have indicated the possible effectiveness of omega 3 fatty acids, n-acetylcysteine, ningdong granule, and 5-ling granule, although there is not sufficient data available in the literature (Quezada & Coffman, 2018).

Novel and Experimental Alternatives

There is growing public interest in cannabinoids and marijuana for use in Tourette syndrome treatment. Patients report improvement in tics, but the response is difficult to substantiate. A Cochrane review reported that definite conclusions on the efficacy of cannabinoids in treatment cannot yet be drawn (Curtis, et al., 2009). There were significant improvements reported in the use of ecopipam at eight weeks, with adverse effects of sedation, fatigue, insomnia, anxiety, headaches and muscle twitching. Tetrabenazine also evidenced efficacy in the range of moderate to marked improvements, with side effects of drowsiness,

parkinsonism, depression, and alcathisia (a movement disorder characterised by a feeling of inner restlessness and inability to stay still that predominantly affects the legs). In the US tetrabenazine now carries a warning for risk of depression and suicidality (Quezada & Coffman, 2018).

In conclusion, when appropriate pharmacotherapy is selected and implemented, most patients with Tourette syndrome can achieve full potential and lead a normal life. It is important that pharmacotherapy be tailored to the individual patient's needs.

References

Cothros, N., Medina, A., & Pringsheim, T. (2020). Current pharmacotherapy for tic disorders. *Expert Opinion on Pharmacotherapy, 21(5),* 567-580

Curtis, A., Clarke, C.E., & Rickards, H.E. (2009). Cannabinoids for Tourette syndrome. *Cochrane Database Systematic Review,* 4:CD006565

Jankovic, J., Jimenez-Shahed, J., Brown, L.W. (2010). A randomized double-blind, placebo-controlled study of topiramate in the treatment of Tourette syndrome. *Journal of Neurol Neurosurgical Psychiatry, 81(1),* 70-73

Jankovic, J. (2020). Treatment of tics associated with Tourette syndrome. *Journal of Neural Transmission.* doi:10.1107/s00702-019-02105-w

Marras, et al., (2001), Botulinum toxin for simple motor tics: A randomized, double-blind, controlled clinical trial. *Neurology, 56(5),* 605-610

Martino, D. (2020). Update on the treatment of tics in Tourette syndrome and other chronic tic disorders. *Movement Disorders, 22,* 10

McCann, L.J., & Newell, S.J. (2006). Survey of pediatric complementary and alternative medicine use in health and chronic illness. *Arch Dis Child, 91,* 173-174

Patel, H., Kieuhanh, N., Lehman, M.S., Gayatra, M., Duda, L., Byler, D., & Kumar, A. (2020). Use of complementary and alternative medicine in children with Tourette syndrome. *Journal of Child Neurology,* 1-5

Pringsheim, T., Holler-Managan, Y, Okun, M.S. (2019). Comprehensive systematic review summary: Treatment of tics in people with Tourette syndrome and chronic tic disorders. *Neurology. 92(19),* 907-915

Qi, H., Liu, R., Zhen, W., Zhang, L., Ungvari, G.S., Chee, H.N., Wang, G., & Xiang, Y.T. (2020). Efficacy and safety of traditional Chinese medicine for Tourette syndrome: A meta-analysis of randomized controlled trials. *Asian Journal of Psychiatry, 47,* 101853

Roessner, V., Plessen, K.J., Rothenberger, A. (2011). European clinical guidelines for Tourettte syndrome and other tic disorders. Part II: Pharmacological treatment. European Child Adolescent Psychiatry, 20(4). 173 – 196

Zelnik, N. (2020). Drug and non-drug treatment of Tourette syndrome. *Current Drug Therapy, 15(2),* 132-142