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Is the Use of the Chinese Herbal Medicine, Ningdong granule, a Safe and Effective Alternative to Haloperidol for the Treatment of Tic Symptoms in Pediatric Patients with Tourette Syndrome (TS)?

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Is the use of the Chinese herbal medicine, Ningdong granule, a safe and effective alternative to Haloperidol for the treatment of tic symptoms in pediatric patients with Tourette Syndrome (TS)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE

The objective of this selective EBM review is to determine whether the Chinese herbal supplement, Ningdong granule, is a safe and effective alternative to haloperidol for the treatment of tic symptoms in pediatric patients with Tourette Syndrome.

STUDY DESIGN

Systematic review of three randomized controlled trials published in 2009, 2010, and 2012.

DATA SOURCES

Three randomized controlled trials were obtained using PubMed.

OUTCOMES MEASURED

Efficacy of Ningdong granule (NDG) as compared to control groups based on decrease in tic severity and frequency as reported by Yale Global Tic Severity Scale as well as safety, as evidenced by prevalence of adverse drug reactions (ADRs) as compared to control groups.

RESULTS

Li et al. (2009), Wang et al. (2012), and Zhao et al. (2010) all demonstrated improvement in a majority of the subjects' tic symptoms while decreasing ADR's from treatment with Ningdong granule compared to haloperidol.

CONCLUSION

Evidence to support the efficacy of Ningdong granule to safely treat tic symptoms in pediatric Tourette Syndrome patients is strong now, due to a relevant subject population, and consistent standard of measurement. The data strongly supports the efficacy of Ningdong granule as an alternative method of treating tic symptoms in pediatric patients suffering from Tourette Syndrome.

KEY WORDS
Tourette and alternative therapy and Ningdong

INTRODUCTION

Tourette Syndrome is a neuromuscular disorder, onset early in childhood, that causes uncontrolled vocal and motor tics ranging from mild to severe.[1,2,3,4] While the exact number of children with Tourette Syndrome is unknown, a CDC study has shown that it affects up to 1 in every 360 children.[4] DSM diagnosis requires two motor tics and at least one vocal tic feature occurring for at least a year, prior to age 18 that cannot be attributed to some other medical condition or medical treatment; the diagnosis is made at an average age of 7.[4] The disorder often lasts into early adulthood (5-18 years old) and often attenuates by the time the child reaches adulthood.[4] The exact etiology of Gilles de la Tourette Syndrome (TS) is unknown, however it is believed that there are multiple complex genetic, environmental and developmental factors that all contribute to the frequency and severity of tic symptoms in patients.[4,5] Symptoms in patients can be socially, educationally and interpersonally impairing, thus leading to treatment for co-morbid conditions as well.[3] However, in some patients tics can be life threatening, as in malignant Tourette Syndrome, or can last throughout their lives.[1] This systematic review attempts to determine whether or not the Chinese herbal supplement, Ningdong granule (NDG), is a safe and effective alternative to haloperidol for treating tic symptoms in pediatric patients. This paper evaluates three randomized control trials (RCT), taking place in China, comparing Ningdong granule versus haloperidol, Ningdong granule with haloperidol, and placebo alone.

In the United States, no solid answer as to how many children or adolescents are affected, nor how many healthcare dollars are spent on TS because in many cases there are co-morbid obsessive compulsive or ADHD diagnoses that are more often treated and insurance billed for.[5] While the CDC estimates 1 in 360 children have TS, it is also thought the actual prevalence may

be twice that based on other studies.[5] For cost, TS has been lumped into the $267 billion in annual mental health costs for mental disorders in children.[5] Also, there is no one treatment to track for TS as there are multiple medications used, as well as behavioral interventions like Cognitive Behavioral Intervention for Tic therapy (CBIT). The exact number of office visits for TS is ambiguous for the same reasons.

While the exact cause of TS is not known, it seems to have a strong genetic link affecting mainly non-Hispanic white males with various biological, mental and environmental factors being identified as risk factors.[4] 86% of Tourette Syndrome diagnoses include a comorbid diagnosis of obsessive compulsive disorder (OCD) or attention defecit hyperactivity disorder (ADHD).[6] The gene link appears to be dominant with 50% of offspring exhibiting the trait and males in general are 3 times more likely to exhibit symptoms of TS than females.[6]

It appears that the attenuation of dopamine receptors calms tic symptoms and therefore, conventionally, traditional antipsychotic medications that work on DA such as haloperidol are used in the management of symptoms in Tourette Syndrome.[7] It is known that these medications can cause sometimes severe side effects such as extra pyramidal symptoms, akathisia, QT prolongation, sedation and weight gain; for these reasons patients often discontinue their use.[1,2,3,7] Newer methods of treatment include habit reversal therapy, CBIT, psychotherapy, acupuncture and herbal medicine.[1,2,3]

OBJECTIVE

The objective of this selective EBM review is to determine whether the Chinese herbal supplement, Ningdong granule, is a safe and effective alternative to haloperidol for the treatment of tic symptoms in pediatric patients with Tourette Syndrome.

METHODS

This systematic review consists of three randomized controlled trials which meet the specific requirements for measuring efficacy and safety of Ningdong granule (NDG) in addition or compared to haloperidol or placebo alone. The first randomized control trial was a 3 month, two group, double-blind study comparing the decrease in tic severity and ADRs of Ningdong granule plus haloperidol to haloperidol alone. Both NDG/haloperidol and haloperidol were used at therapeutic doses. The second randomized control trial was an 8-week, three group, double-blind study that compared the decrease in tic severity and ADRs of NDG to NDG + haloperidol to haloperidol and placebo alone. The third trial was an 8-week randomized, double blind control trial comparing NDG to placebo. The study population of all three trials consisted of children or adolescents at or under the age of 18 and who were clinically diagnosed and met the DSM-IV criteria for Tourette Syndrome. The populations excluded from these studies were patients over the age of 18 years old, had comorbid conditions requiring medication, history of recent or current drug abuse, or had tics that could be accounted for by other medical conditions.

Keywords used in the research for these studies were Tourette and alternative therapy and Ningdong. All articles used in this research were peer-reviewed journals and were found via PubMed. The articles were published in English and in Chinese. To be selected, the articles

researched had to meet several inclusion criteria including: being relevant to the clinical question proposed, published in 2001 or later, must have been primary research and addressed patient oriented outcomes (POEM). Criteria for exclusion included articles published prior to the year 2001, articles that were not primary research in nature (other reviews) or if they focused on disease oriented outcomes (DOE). Statistics used in the articles include p-values, NNT, NNH, RRI, RBI, and ABI. Table 1 below displays the demographics and characteristics of the studies that were reviewed and used.

Table 1: Demographics & characteristics of included studies

Study	Type	#Pts	Age (yrs.)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Li[1] (2009)	Double Blind RCT	60	<18	Pediatric pts dx with TS	- > 18 years - not matching the standard of inclusion - habitual spasm - complicated with other ds in an unstable state requiring other medications	0	Haloperidol in combination with dosage-form of NDG, 6 g in each packet, medicated by dissolving in boiled water for oral intake BID, at the dose of 3 g each time for children younger than 6 years, 6 g for those between 7-11 years and 9 g for those older than 12 years.
Wang[2] (2012)	Double Blind RCT	120	6-18	Pediatric pts dx with TS	- pts who took TS medications within 6 mos. of study - pts who had hx of seizures, CVD, organic brain d/o - current abuse or dependence on drugs w/in 6 mos.	3	NDG group assigned to receive NDG 5 mg/kg/day and one placebo similar in appearance and taste to Haloperidol for 8 weeks.
Zhao[3] (2010)	Double Blind RCT	68	7-18	Pediatric pts dx with TS	- intelligence quotient (IQ) < 70 per the Wechsler	4	Subjects received either an oral dose of 1 g/kg per day (36 g/day max) of NDG

					Intelligence Scale for Children;19 - tic syndromes caused by other ds - dysfunction of the liver, kidney or other organs - a motor or phonic tic score < 10 on the Chinese Yale Global Tic Severity Scale (YGTSS)		powder or placebo formulated to look identical to the NDG to ensure double blinding the medication being administered.

OUTCOMES MEASURED

All studies used measured the desired outcomes of tic severity by diminution rate of Yale Global Tic Severity Scores (YGTSS) and safety of the drug by way of ADR prevalence. Participants were given the questionnaires for tic severity prior to the study, immediately after the study and in the first study, long term results were measured at variable time intervals after the study. In all studies, safety was measured by recording existence of adverse drug reactions (ADRs) during treatment in all groups. In the Li study, tic severity was recorded at baseline, immediately after treatment and then at 6 months for long term efficacy; safety was measured in ADRs reported and observed vs. control at each interval. In the Wang study, tic severity was assessed at baseline and every two weeks thereafter until study completion at week 8; safety was measured by reported and observed ADRs at any time during the study. In the Zhao study, tic severity was measured at baseline and after 4 and 8 weeks of treatment; safety was measured by reported and observed ADRs at any time during the study.

RESULTS

In all three randomly controlled trials, the efficacy and safety of Ningdong granule is compared to placebo or haloperidol. In the Li study, a total of 60 patients entered the study and all patients completed the study. The exclusion parameters for this study included patients who were older than 18, did not match the DSM-IV diagnosis for Tourette Syndrome, had habitual spasm, or had comorbid disease in an unstable state requiring medication. The patients were all pediatric patients with tic severity at baseline ranging from mild to severe, including both males and females in proper proportion. The mean age of patients was 9.59 years.[1] Patients were randomized into two groups by randomizing digital table method where n=30 in the control and n=60 in the treated group. Ningdong granule used in this study was Shanghai Xinyi Jiufu Pharmaceutical Co. Ltd., batch No. 061210. Group 2 control was treated with haloperidol alone at 0.5mg twice per day, titrating to therapeutic doses for each individual. The treated Group 1 was given haloperidol in the same fashion, but supplemented with 3g/dose twice daily for children ≤6 years, 6g/dose for ages 7-11 and 9g/dose for ≥12 years of age. In Group 1 the clinical efficacy was found to be markedly effective in 36 (60.0%), effective in 21 and ineffective in 3, with a total effective rate of 95.0%. For the 30 patients in Group 2, data results were 9 (30.0%), 13, 8, and 73.3%, respectively. Comparing the markedly effective rate and the total effective rate between the groups showed significant differences ($P<0.01$, Table 2). For ADRs in Group 1, drowsiness n=3, lassitude n=2 and poor appetite n=3, the overall ADR rate was 13.3%, while in Group 2, drowsiness n=4, constipation n=1, lassitude n=3, poor appetite n=1 and akathisia n=2, with an overall ADR rate of 36.7%. There was statistical significance for ADRs shown ($\chi^2=6.54$, $P<0.05$). This study was double blind and there were no limitations to this study.

Table 2. Li Study: Comparison YGTSS Score, NDG + Haloperidol vs. Haloperidol

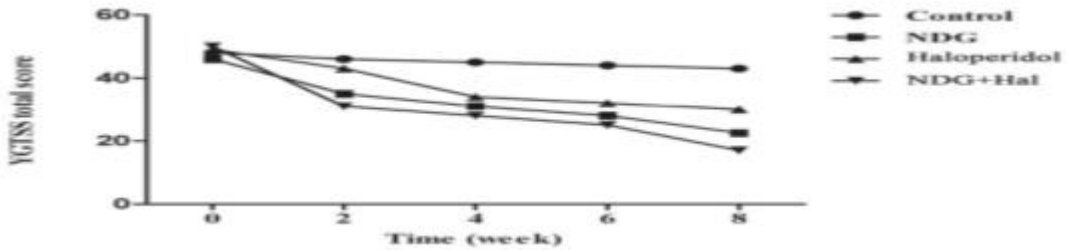
Group	Case	Markedly Effective	Effective	Ineffective	Total Effective
Treated 1	60	36 (60.0*)	21 (35.0)	3 (5.0*)	57 (95.0*)
Control 2	30	9 (30.0)	13 (43.3)	8 (26.7)	22 (73.3)
χ^2		7.20	2.63	6.85	6.85

Note: *P<0.01 when compared with control group

In the Wang study, 120 patients from Provincial Hospital between the ages of 6-18 with TS were recruited for the study. 3 patients did not submit reports for ADRs, 2 in the placebo group and 1 in the NDG only group. Exclusion parameters included patients who took TS medications within 6 months of the study, patients who had history of seizures, cardiovascular disease, organic brain disorders and those who currently, or within the last 6 months, abused or were dependent on drugs. The study was done by using a digital random table generator to randomly assign patients to 4 equal groups (n=30) with Control receiving 2 placebo pills, NDG receiving Ningdong granule and a placebo, haloperidol receiving haloperidol and placebo and the Ningdong + haloperidol receiving both drugs. The NDG used was No. 20090412, 999 Co. Ltd., Shenzhen, China. The mean age of patients was 10.2 years old and there was no significant difference in weight, age or gender of the groups. Patients in the placebo controlled group had no significant change in YGTSS total tic score, at each time point when compared to baseline ($P > 0.05$). However, two weeks into the study, patients being treated in the three other groups showed a significant reduction in total YGTSS scores, thus lower tic severity ($p < 0.05$), with the NDG + Hal group the most significantly reduced ($p < 0.01$) (Table 3). While no serious side effects were reported overall, patients experiencing sedation, extrapyramidal symptoms, QT prolongation and anxiety for NDG vs. haloperidol were found to be significantly less ($p<0.05$)

(Table 4). This study had one limitation for this in that efficacy was assessed over the short term.

Table 3. Wang Study: Comparison of YGTSS Scores in all Groups



*significance reported at P < 0.05

Table 4. Wang Study: Clinical complications and side effects

ADR	Control (n=28)	NDG (n=29	Hal (n=30)	NDG + Hal (n=30)
Sedation	1 (3.5%)	3 (10.3%)*	10 (33.3%)	12 (40.0%)
Weight gain	2 (7.0%)	2 (6.9%)	4 (13.3%)	5 (16.7%)
EPS	0	0*	5 (16.7%)	5 (16.7%)
QT Prolongation	0	0*	5 (16.7%)	5 (16.7%)
Nausea	0	3 (10.3%)	4 (13.3%)	4 (13.3%)
Headache	0	1 (3.4%)	4 (13.3%)	6 (20.0%)
Anxiety	1 (3.5%)	0*	6 (20.0%)	4 (13.3%)
Increased Appetite	0	4 (13.8%)	4 (13.3%)	7 (23.3%)

Note: * significance P<0.05

The Zhao study evaluated the efficacy and safety of Ningdong granule vs. placebo over an 8-week randomized, placebo controlled, double blind trial. 68 pediatric patients between the ages of 7-18 with TS were recruited in this study; 3 patients in the placebo group and 1 in the NDG group did not complete the full course of treatment and were excluded from analysis. Exclusion criteria included those who had IQ < 70, tic syndromes caused by other disease, persons with liver, kidney or any other organ dysfunction, and finally any applicant whose baseline was <10 on the YGTSS. Patients were randomly assigned to either a treatment group

(n=33) receiving NDG 1g/kg/day (36 g/day max) or the placebo group (n=31) and given starch formulated to be identical to NDG at the same frequency. The Ningdong granule used was lot No. 20051017, manufactured by the Pharmaceutical Department of the Provincial Hospital Affiliated to Shandong University. There was no significant difference between the groups for age, weight, gender, previous pharmacotherapy use or baseline YGTSS score (P>0.05). Mean baseline YGTSS score for Treatment group was 23.00 ± 7.34 and baseline for the placebo group was 22.42 ± 6.42. YGTSS scores were measured at baseline, 4 and 8 weeks. At each interval after treatment was started, there was found to be a significant reduction in tic symptoms from baseline in the NDG treatment group compared to the placebo group, but most notably so at the end of eight weeks (P<0.001). There was little change in mean total YGTSS score (22.42± 6.42 to 20.00 ± 6.12) in the placebo group from baseline to the end of the study. There were no serious drug reactions reported during the study in either test group, however in the NDG treatment group there were two patients who experienced a decreased appetite and one who experienced constipation compared with none in the placebo group. Less than 10% of the treatment population experienced any type of ADR, which is minimal compared to the potentially serious side effects of traditional antipsychotics like haloperidol.[2,3] This study had several limitations in that it was short term, single centered study and was assessed only by the decrease in YGTSS score.

Table 5. Zhao Study: YGTSS total tic score change for NDG vs. placebo

Group	**Case**	**Mean Baseline YGTSS total tic score**	**Mean week 8 YGTSS total tic score**
NDG Treatment	33	23.00 ± 7.34	13.48 ± 7.25
Placebo Control	31	22.42 ± 6.42	20.00 ± 6.12
Statistical significance		P>0.05	P<0.001

DISCUSSION

This systematic review assessed the efficacy and safety of the Chinese herbal supplement, Ningdong granule vs. traditional haloperidol treatment in reducing tic symptoms in pediatric Tourette syndrome patients. Currently, herbal remedies are not widely used to treat TS in the United States. The results of these three studies show that NDG is an effective alternative to haloperidol with a much lower adverse drug reaction profile. While some ADRs for NDG do exist, they are fewer and far less severe reactions as compared to haloperidol. Drug to drug interactions were not accounted for in any of the studies as current drug use or medication for other diseases were criteria for exclusion.

There were several limitations noted with the studies reviewed. First, insurance in the United States will not currently cover herbal remedies and the FDA does not regulate the production of herbal supplements. This is a problem for this type of study in the U.S as well as for consistent production and dosing of the supplement long term. While the Ningdong granules used were produced by licensed Chinese pharmaceutical companies and were proven to be consistent in each trial, there was variation in the ingredients used, concentrations of ingredients and the dose administered between the three studies. Also, powdered human placenta was used in the formulation of the granule in two studies, which is currently against U.S. FDA regulation. Second, the results and outcomes were measured in the short term only for two of the three studies. The Li study also assessed efficacy and ADRs six months after the study but were not required to answer the question posed in this review. Last, all studies used only one method, the Yale Global Tic Severity Scale, to assess effectiveness in reducing tics in the patient population.

CONCLUSION

Ningdong granule is a safe and effective alternative therapy to haloperidol in the relief of tic symptoms in pediatric aged patients diagnosed with Tourette Syndrome. All three studies included showed significant evidence improvement in YGTSS scores and thus total tic symptoms while having significantly fewer adverse drug reactions. Although these studies did not compare Ningdong to other off-label drugs used for the treatment of tics, NDG has been shown to be more effective and more safe than the traditional antipsychotics prescribed. Even with different amounts and small variation in ingredients between manufacturers.

While the Ningdong granules used were produced by licensed Chinese pharmaceutical companies and were proven to be consistent in each trial, there was variation in the ingredients used, concentrations of ingredients and the dose administered between the three studies. It would be beneficial to have a normalized ingredient profile for future studies so that results could be more easily replicated by future studies. Future studies should be multi-centered comparing multiple drugs to NDG and assess over the long term while utilizing multiple assessment tools to measure improvement in tic symptoms and overall psychological well-being. Tools such as Children's Yale-Brown Obsessive Compulsive Scale (CY-BOC), Children's Depression Inventory (CDI), Clinical Global Impression (CGI-I) and the Multidimensional Anxiety Scale for Children (MASC) would be beneficial in a multi-centered, long term study.[3]

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