22q11 Deletion syndrome and neurotransmitter systems in unchallenged and challenged conditions
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Chapter 1

Challenge and therapeutic studies using alpha-methyl-para-tyrosine (AMPT) in neuropsychiatric disorders: a review

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ABSTRACT

Alpha-methyl-para-tyrosine (AMPT) temporarily inhibits tyrosine hydroxylase, the rate limiting step in the dopamine biosynthesis cascade. AMPT has been approved for clinical use in phaeochromocytoma in 1979. Recently however, AMPT has been increasingly employed as a pharmacological challenge in acute dopamine depletion studies including neuroimaging studies. The use of this exciting challenge technique allows us to increase our understanding of dopaminergic neurotransmission in the brain. In addition, there have been clinical reports that AMPT may be useful to treat movement disorders like dystonia, dyskinesia and Huntington’s chorea, psychiatric disorders like mania, psychosis, obsessive compulsive disorder and substance abuse as well as behavioral problems in 22q11 deletion syndrome. In this review we will discuss the effects of AMPT in challenge studies that have been reported in humans. Furthermore we will review all studies reporting therapeutic effects of AMPT in neuropsychiatric disorders and adverse effects associated with AMPT use reported in both challenge and therapeutic research.
INTRODUCTION

Depletion of selected monoamines, such as dopamine (DA) and serotonin, is a method that is used as a way of elucidating the pathogenesis of neuropsychiatric disorders. In these so called “challenge studies” different techniques are used to acutely and temporarily lower the levels and consequently the function of monoamines. The currently most established depletion tests for norepinephrine (NE) and DA are phenylalanine/tyrosine depletion (APTD) and alpha-methyl-para-tyrosine (AMPT). Depletion of serotonin (5-HT) is mainly achieved by acute tryptophan depletion (ATD) and para-chlorophenylalanine (PCPA) [10].

Many neuropsychiatric diseases have underlying DA and or NE abnormalities. For example schizophrenia and psychosis are hypothesized to be related to mesolimbic and striatal hyperdopaminergic states according to the DA hypothesis [92]. Other disorders related to DA dysfunction include movement disorders such as Parkinson’s disease, dystonia, dyskinesia and Huntington’s disease, and neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD), addiction, and obsessive compulsive disorder (OCD).

AMPT (figure 1) is a specific competitive inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of DA (and NE) from tyrosine [30]. Studies of human cerebrospinal fluid after acute AMPT administration found a 50–70% decrease in the DA metabolite homovanillic acid (HVA; 3-Methoxy-4-hydroxyphenyl acetic acid), and no change in the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) [14,15]. Urinary levels of the NE metabolite vanillylmandelic acid (VMA) and 3-methoxy-4-hydroxy-phenylglycol (MHPG) are decreased by 25-50% [14,29]. The DA depleting effect of AMPT is being used clinically in the management of phaeochromocytoma, to reduce catecholamine-induced pre- and intra-operative complications. Moreover, by using AMPT it is also possible to specifically investigate DA/NE neurotransmitter systems through challenge paradigms.

Figure 1.
Alpha-methyl-para-tyrosine (AMPT)
In the past decade, AMPT has been increasingly used as a pharmacological challenge in humans. In addition, observations have been made of potential beneficial effects of AMPT in the treatment of neuropsychiatric disorders. In this review we will discuss the effects of AMPT on humans in neuropsychiatric research and the clinical management of neuropsychiatric disorders.

METHODS
Medical databases (PubMed) were used to identify relevant literature (period between 1965 and May 2008). Keywords used were: “ampt”, “alpha-methyl-para-tyrosine”, “demser”, “metyrosine” and “alpha-methyl-p-tyrosine”. Additionally reference lists of retrieved articles were checked. We included all human challenge and treatment studies relevant to neuropsychiatric disorders found in PubMed. We excluded animal and in vitro studies from the review.

CLINICAL USE OF AMPT
Currently AMPT has only been approved for clinical use in phaeochromocytoma (since 1979), which is a catecholamine-producing tumor of the sympathetic nervous system with an incidence of 0.2-0.4% in hypertensive patients [102]. Most of these tumors occur in the adrenal glands and secrete NE and epinephrine but they may also rarely secrete L-DOPA and/or DA. The typical manifestation is sustained or paroxysmal hypertension, with the triad of severe headaches, palpitations and diaphoresis resulting from hormone excess [83]. Before the introduction of catecholamine blockade, surgical resection of phaeochromocytoma was associated with a mortality rate of 24 to 50% [57,81]. This was due to the fact that intra-operative catecholamine release, caused by anesthesia or tumor manipulation, induced severe hypertension, arrhythmia’s and stroke.

Adding AMPT to the alpha-adrenergic blockade with phenoxybenzamine has been associated with the need for less intra-operative medication for the control of blood pressure, lower intra-operative fluid requirements, and lower blood loss and decreased surgical morbidity [78,88]. In recent years surgical mortality has dropped to 0% to 2.9% [50]. Nevertheless, sometimes hypertensive crisis still occurs when AMPT is not combined with adequate alpha-blockade [41,43,82]. Although AMPT has demonstrated its effectiveness in the management of patients with phaeochromocytoma in reducing symptoms [29], it does not have a significant beneficial effect on essential hypertension. Thus the clinical use of AMPT in the treatment of hypertension seems limited to hypertension induced by catecholamine producing phaeochromocytoma, and is based on depleting the causal agent for the associated symptoms, NE.

Some reports have suggested that AMPT may have beneficial effects in the treatment of other conditions. Glaucoma is a group of diseases characterized by progressive damage of the optic nerve involving loss of retinal ganglion cells in a characteristic pattern of optic neuropathy. Intraocular
pressure is a significant risk factor for developing glaucoma. It is the second most common cause of irreversible blindness in the world and affects more than 70 million people worldwide [22]. Although glaucoma is frequently mentioned in literature as an indication for AMPT use, there are no studies to support this. Engelman discussed the issue briefly in his study where two patients with glaucoma were included, and found no improvement [29]. In a more recent study AMPT appeared to have a beneficial effect in vitro on hyperpigmentation [28], a side effect of the anti-glaucoma drug latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-PGF$_2$$\alpha$-isopropyl ester), but another study could not replicate this [58]. No other studies were found, and thus it seems fair to conclude that there is no evidence that AMPT has beneficial effects on patients with glaucoma.

**AMPT AS A PHARMACOLOGICAL CHALLENGE IN NEUROPSYCHIATRIC RESEARCH**

Challenge studies using AMPT are abundant, covering a wide area of disciplines both in human and in animal populations. In the following paragraph we will discuss all human studies with relevance to neuropsychiatric disorders. Animal and in vitro studies were not included, as most researched highly specific physiological and pathological biochemical pathways which are beyond the neuropsychiatric scope of this review. Common AMPT depletion procedures administer a total amount of 4500 – 8000 mg of AMPT in a 25 to 48 hour study period [10]. The first challenge studies date back to the 1970’s. In that period Shopsin studied depressed patients who showed an antidepressant response to the tricyclic drug imipramine, to elucidate the biochemical pathway behind this antidepressant [86]. AMPT did not cause relapse of depression and thus Shopsin concluded that serotonergic mechanisms were most likely involved in the antidepressant effects of imipramine (N-(p-Dimethylaminopropyl)iminodibenzyl) [86].

**Healthy Subjects**

An AMPT challenge using common doses does not usually induce depressive symptoms in healthy, but may have a slight negative effect on mood, which relatively (and absolutely) increases when combined with sleep deprivation [42,64,65]. Furthermore AMPT has been reported to decrease attention, alertness, happiness and increase sleepiness, tension and anger [35,52,56,64,65,85,93,95]. Most symptoms can be reversed by administering L-dopa and thus seem to be dopaminergically modulated [67]. Additionally, Tychsen [91] reported an AMPT-induced increase in saccadic eye movements in a small study (N=3) when administering 3g/day for 3 consecutive days.

Acute administration of AMPT also has a negative effect on subjective wellbeing. Subjects showed declining scores on mental functioning, emotional regulation and physical functioning, as measured by the Subjective Well-being Under Neuroleptic Treatment Scale (SWN) [12]. Transient extrapyramidal
side effects (EPS) of varying severity (hypokinesia, rigidity, tremor, salivation) have been commonly reported after acute DA depletion with AMPT [24,29,35,52,56,62,95].

Furthermore, increased anxiety is often reported [24,29,52,65], again varying from slight increases to recurrent panic attacks [35,63] requiring subject withdrawal from the study, but symptoms never persist after discontinuing AMPT medication. Catecholamines thus appear to be involved in anxiety regulation, since administering L-dopa also reverses AMPT-induced anxiety [67]. However other studies did not find increased anxiety after AMPT [56,95], and no apparent dose-response effect can be distilled from the studies. Healthy subjects were also reported to display transient decreases in total sleep for a few days after stopping AMPT [3,4,21,29,87,100].

Imaging studies have shown that AMPT depletion provides a non-invasive method for estimating synaptic DA concentrations in healthy subjects using positron emission tomography (PET) [95] and single photon emission computed tomography (SPECT) [35,56]. The effect of DA depletion can be measured in-vivo using radiotracers for the D2 receptor. Indeed, acute DA depletion induced by AMPT leads to an increased D2 receptor binding, but does not significantly alter D1 receptor binding [94]. Data suggest that endogenous DA occupies between 20% and 30% of D2 receptors in healthy subjects which is reflected in an increase in D2 binding potential following DA depletion. Importantly, it has been argued that such an increase cannot be explained by D2 receptor up-regulation, which would require longer than a week of DA depletion [56,73]. Relatively low doses of AMPT can be used to obtain adequate results [12], while producing acceptable levels of side effects. A recent PET study [23] reported that [(18)F]fallypride combined with AMPT challenge may be unreliable for estimating tonic or baseline DA levels in humans, as no significant change in binding potential was found in striatal and extrastriatal regions after AMPT administration. These findings were in contrast with another recent study which found that a higher dose of AMPT (66 mg/kg/24h vs. 23 mg/kg/24h; total dose was 71 mg/kg vs. 43 mg/kg) significantly increased the binding potential in the caudate nucleus, putamen, ventral striatum, and substantia nigra [84]. Although the dose was lower, Cropley et al [23] reported similar plasma levels of AMPT but absent side effects. These results are also in contrast to previous SPECT and PET studies using different radioligands, which reported increases of D2 radioligand binding in the striatum after an AMPT challenge using [123I]IBZM [56] or [11C]raclopride [94,95], and in the temporal cortex with [123I]epidepride [35]. These conflicting results may be the result of small sample size, interference with the amphetamine challenge one week before in Cropley’s study, dose related, or due to different characteristics of the radioligands used.

Prolactin (PRL) is commonly used as a marker for DA depletion, as DA inhibits the release of PRL at the level of the pituitary gland [34]. Treatment with AMPT consistently produces two- to four-fold increases in PRL levels [94] although DA is not the only factor controlling PRL levels, and there is no direct relation between DA levels in the hypophysial stalk and serum PRL levels [34]. Women display higher AMPT induced PRL secretion than men, possibly explained by the PRL synthesis promoting effect of estradiol on the pituitary gland [104].
Melatonin (5-methoxy-N-acetyltryptamine), and its urinary metabolite 6-hydroxymelatonin (6-MS) are regulated by noradrenergic neurons located in the sympathetic superior cervical ganglion via NE-induced stimulation of postsynaptic beta-adrenergic receptors on the pineal gland [71]. Melatonin and 6-MS were reported to be a superior marker for NE depletion by AMPT compared to MHPG as there are sex differences in MHPG secretion and only 20-65% of circulating MHPG is derived from the brain [52,103,104]. The same research group investigated the possibility that leptin would be modulated by NE, but found no evidence for this when performing an AMPT challenge on ten healthy individuals [105].

Although short-term effects of AMPT include TSH stimulation through the decrease in DA’s inhibiting effect [76,79], prolonged use of AMPT was also reported to inhibit thyroid-stimulating hormone (TSH) secretion and significantly attenuate the circadian rhythm of TSH [106]. This is probably caused by NE’s inhibitory effect on thyroid-releasing hormone (TRH); animal research has indicated that the depletion of NE occurs later in time than DA depletion by AMPT [51].

In conclusion, AMPT challenge has little effect on mood but can cause transient sedation, EPS and anxiety in healthy subjects, particularly at higher doses.

Mood Disorders
Some patients with a history of medically-treated depression experience a return of symptoms [14,15,29,42,72] after DA depletion with AMPT. This may depend on individual vulnerability to depression [6], but also seems to depend on the mechanism of prior anti-depressant medication. AMPT led to relapse of depression in patients who had been successfully treated with NE reuptake inhibitors (desipramine (N-(3-Methylaminopropyl)iminobenzyl) and mazindol (5-(4-Chlorophenyl)-2,3-dihydro-5-hydroxy-5H-imidazo(2,1-a)isoindole)), but not in those treated with selective serotonin reuptake inhibitors (SSRI) (fluoxetine (dl-N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine) and sertraline ((1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-tetralin-1-naphthalamine)) [25,68,69]. Conversely, when patients received tryptophan depletion, which lowers available 5-HT, relapse only occurred in patients successfully treated with SSRI’s [26]. Moreover, treating patients with an antidepressant with actions on both 5-HT and NE (mirtazapine (6-Azamianserin)) led to partial relapses of depression in most patients [27]. AMPT did not lead to worsening of their condition in the actively ill [7,44,69]. Furthermore, AMPT also seems to induce relapse in seasonal affective disorder [53,75], but did not so in eight bipolar patients who were stable on lithium medication [4]. A recent study [13] showed that the effect of AMPT on prefrontal, orbitofrontal and thalamic metabolism (measured with 18F-FDG PET) could differentiate between patients who would experience a return of depressive symptoms after AMPT depletion and those who would not (all participants were patients with a depression in stable remission on NE re-uptake inhibitors). The patients with a return of symptoms showed a decreased metabolism (from elevated baseline) and the patients without a return of symptoms showed an increase in metabolism (from
Hasler et al [42] also found reduced metabolism in the orbitofrontal region, and reported that this did not differ from healthy controls. In contrast, decreased metabolism was found in the anteroverentral striatum, increased metabolism was found in the right thalamus and left superior temporal gyrus, and no change in metabolism was found in the dorsolateral prefrontal cortex. Furthermore they reported that depressive and anhedonic symptoms induced by AMPT depletion are related to increased activity within the limbic-cortical-striatal-pallidal-thalamic circuitry in remitted depressed patients but not in healthy controls, which provides direct evidence for catecholamine dysfunction in depression. Also, anxiety increased significantly in patients with a depression in remission after AMPT, even though they lacked a history of anxiety disorders.

In conclusion, occurrence of a relapse of depressive symptoms in stable patients after AMPT seems dependent on the mechanism of prior anti-depressant medication and AMPT does not worsen depression in actively ill patients. Brain glucose metabolism in successfully treated depressed patients may predict depressive responses to AMPT treatment, and there is direct evidence for catecholamine dysfunction in depression from challenge studies.

Schizophrenia

Patients with schizophrenia showed a decrease in subjective wellbeing after an AMPT challenge, and those patients who had a history of persistent dysphoria in response to previous neuroleptic therapy had significantly greater dysphoric responses scored on the Drug Attitude Inventory (DAI) and the Addiction Research Center Inventory (ARCI) than patients who did not have such a history [96]. In the same study, Voruganti reported an inverse correlation between subjective responses plus EPS (increases in dysphoria scores on ARCI and DAI and increases on the Barnes Akathisia Scale and Simpson-Angus Scale) and the changes in D2 receptor binding ratios. This suggests that schizophrenic patients with relatively lower (but probably still increased compared to healthy controls) endogenous DA activity are more susceptible to dysphoric response and EPS following DA challenge with AMPT than schizophrenic patients with a relatively higher DA activity. Later research by the same group replicated these results [97]. Abi-Dargham reported an increased D2 receptor availability after AMPT in the schizophrenia group as compared to the control group, which implies that schizophrenic patients have elevated neostriatal DA levels compared to controls [2]. To our knowledge, no challenge studies focusing on D1, D3, D4 or D5 receptor availability have been published, and D2 receptor studies without a DA challenge have conflicting results [1,77]. 22q11 Deletion syndrome (22q11DS) was also reported to have disrupted dopaminergic neurotransmission, which might explain their susceptibility for psychiatric disorders like psychosis and schizophrenia [12]. Thus, AMPT seems useful in elucidating the role of DA in the pathogenesis and susceptibility to side effects of medication of these disorders.
Substance-Induced Disorders
McCann reported differential responses to an AMPT challenge in cognitive measures of speed and impulsivity and of sleep architecture when comparing 25 abstinent 3,4-methylenedioxy-N-methylamphetamine (MDMA, the main component of the recreational drug commonly known by its street name XTC) users to 23 controls [66]. AMPT administration led to more prominent increases in cognitive speed and impulsivity in MDMA users than in controls and MDMA users had less difficulty falling asleep and had larger increases in rapid eye movement (REM) latency following AMPT. This supports the theory that MDMA can lead to subtle functional deficits in brain functions involving reciprocal 5-HT/catecholamine interactions.

AMPT AS A THERAPEUTIC IN NEUROPSYCHIATRIC RESEARCH
Dystonia and Dyskinesia
There have been some reports of beneficial effects of AMPT in patients with movement disorders including dystonia, dyskinesia, and akathisia, although most are case-reports. A recent paper presented three case studies in which AMPT was used in patients suffering from dystonia and dyskinesia. In the first case, AMPT was added to antipsychotic treatment in a woman who after brain injury had hallucinations and “attacks” of painful dystonia. She had only mild dystonia once a week after adding AMPT, which deteriorated when AMPT was stopped. In the second case tardive dystonia improved after adding AMPT in a retarded woman who had used clozapine (8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo(b,e)(1,4)diazepine). In the third case tardive dyskinesia was successfully treated with AMPT [5].

Treating dystonia with AMPT was also studied by Fahn [33], who reported little benefit in an unspecified number of patients. Lang et al [54] reported that some individual dystonic patients seemed to benefit from the addition of AMPT, but that the results overall were disappointing. Interestingly, McCann reported that 5 of 24 healthy volunteers even developed dystonia when administered AMPT at a total dose between 5,25 and 6,75 grams [62]. The paradoxical fact that AMPT is used to treat dystonia but that AMPT can also induce it may be explained by Hornykiewicz’ view that any disturbance in the balance between striatal DA, NE, serotonin, and acetylcholine systems that leads to a functional overactivity of cholinergic brain mechanisms may be sufficient to cause dystonia in susceptible individuals [46].

In patients with tardive dyskinesia, Gerlach et al reported a decrement in frequency and amplitude, but an increase of duration of tongue protrusion and/or mouth opening after treatment with AMPT. In contrast, biperiden (an anticholinergic agent: 3-Piperidino-1-phenyl-1-bicycloheptenyl-1-propanol) had opposite effects [36-38]. Fahn et al published some promising results on the treatment of tardive dyskinesia with AMPT. He used AMPT on 14 patients diagnosed with (neuroleptic-induced) tardive dyskinesia and akathisia in an uncontrolled open label trial and reported improvement when using
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AMPT as a supplement to reserpine (3,4,5-Trimethoxybenzoyl methyl reserpate) treatment, which is a pre-synaptically acting DA depletor [33]. He reported on this earlier [31], when he treated 7 patients with reserpine and AMPT, (5 responded to blindly substituting AMPT for placebo and back) and later on reported more long-term results [32]. The last report concluded that the addition of AMPT to the pre-synaptic DA depleters reserpine or tetrabenazine (TBZ) increased the potency of the treatment.

It has been proposed, as a possible biochemical pathway, that the additive effect of AMPT in dystonia and tardive dyskinesia may lie in the fact that AMPT mainly limits DA synthesis in the cytosolic pool (or newly synthesized pool) of dopaminergic cells, and that reserpine and TBZ prevent DA uptake into the vesicular pool (stored pool) [49,101].

In conclusion, AMPT appears to have beneficial effects on patients with tardive dyskinesia, and may potentiate reserpine and TBZ treatment, nevertheless evidence is scarce and there is obvious need for protocolised double-blind, placebo-controlled trials to confirm this. AMPT appears to benefit some individual patients with dystonia, although the results overall are not promising.

Huntington’s Chorea
Lang [54] reported that of 9 patients with Huntington’s chorea, 3 were unable to tolerate the addition of AMPT to their TBZ or reserpine treatment and two had no change in symptoms, but 4 experienced a marked improvement in movements scores compared to their scores on TBZ alone. Placebo substitution yielded significant increases in chorea in all 4 patients, and as an add-on, AMPT appeared to potentiate the effect of TBZ, as the mean TBZ dose could be reduced from 142mg to 58mg after addition of AMPT [54]. Already in the 1960’s Birkmyer reported a decline in chorea in six patients within a day after daily administration of 200 mg AMPT intravenously [9] and total absence of chorea in one of five subjects 60 minutes after administering 500 mg AMPT intravenously [8].

West Syndrome
Twelve children with newly diagnosed untreated infantile spasms, also known as West Syndrome, were treated with AMPT. Response to therapy was determined objectively with 24-h polygraphic/video monitoring techniques and was defined as cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. Two of 12 patients treated with AMPT responded to therapy and one patient had a return of symptoms after AMPT medication was stopped [47], which provides evidence that AMPT had a beneficial role on the symptoms in this disorder.
Mania
In two early studies AMPT appeared to have a beneficial effect on some patients with a manic episode, although studies were very small and open-labelled [14,15]. After withdrawal of AMPT some patients experienced a transient relapse of hypomanic symptoms and less need for sleep [4,14,16]. Interestingly, decreased need for sleep, decreased total sleep hours and decreased REM sleep are also reported in healthy subjects [3,4,21,29,87,100]. Equally, depressed patients displayed significant decreased sleep and even hypomanic symptoms after stopping AMPT [16]. This effect had no correlation with the dose of AMPT [16] and was hypothesized to be related to changes in melatonin secretion [103]. Bunney et al reported that post-AMPT hypomanic patients had nearly equal decreases in sleep as post-AMPT non-hypomanic bipolar patients, and thus argued that this decrease cannot be fully explained by an increase in mania [16]. Then again, since healthy subjects and depressed patients also showed decreases in sleep and hypomania post-AMPT, it is tempting to suggest that the “insomnia” is not an isolated symptom but rather part of a hypomanic spectrum, involving a larger portion of subjects. The hypomanic symptoms and the decrease in sleep may be explained by increased sensitivity (hyper- or supersensitivity) of DA receptors following depletion of DA, as proposed by Bunney [4,16]. So although there are some early reports of beneficial effects of AMPT, Brody et al reported it to be inferior to lithium carbonate [14], and no later therapeutic studies were performed in manic subjects. There appears to be a rebound effect after stopping AMPT medication, yielding hypomanic symptoms and/or sleep decrements in manic, depressed and healthy subjects which is hypothesized to be caused by increased DA receptor sensitivity.

Obsessive compulsive disorder
One (double-blind, placebo-controlled) study reported no effect in 6 non-medicated patients with non-tic-related obsessive compulsive disorder (OCD) [59]. To our knowledge, no other AMPT studies on OCD were done. Sweet et al administered AMPT to 6 patients with Tourette syndrome, which induced a sustained dramatic decline of profound movement and vocal tics in one patient for at least a year and improved symptoms in two more for a shorter period [90].

Substance Abuse
As DA is known to be involved in substance abuse, AMPT was also studied for its potential to suppress drug craving and drug dependence. Pozuels reported cessation of amphetamine, methadone and heroin use and in craving in a case report [80] and Jönssen et al reported lowered amphetamine-induced euphoria in patients with AMPT treatment [48]. This lowered euphoria was also observed in relation to alcohol use [3]. Regarding cocaine abuse, Stine’s study, although reporting a trend towards a diminished cocaine-induced “high”, did not provide strong support for the therapeutic potential of AMPT depletion in cocaine abuse [89].
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22q11 Deletion syndrome
There is preliminary evidence that patients with 22q11 deletion syndrome (22q11DS) might profit from AMPT medication. Recently, Boot et al reported beneficial subjective effects of acute AMPT medication [11] and in an earlier small uncontrolled open-label trial [40], three out of four patients continued AMPT after the trial due to increased subjective well-being. Furthermore a recent case report showed reduction of psychotic symptoms and mood lability in a 22q11DS patient who did not respond to regular treatment, and was treated with AMPT [18]. This is interesting as a lot of evidence is pointing to dopaminergic dysregulation, caused by the genetic anomalies in this disorder [12].

Schizophrenia
This anti-psychotic effect of AMPT has also been studied in schizophrenic patients. Carlson’s group [19,20,55,98] consistently showed that addition of AMPT led to reduced doses of concurrent neuroleptic treatment among stable chronic schizophrenia patients. Nevertheless, others could not reproduce these results [21,39,74,97,99], or found the neuroleptic-potentiating effect to be too limited in relation to adverse effects [60,61]. Abi-Dargham reported that high synaptic DA levels predicted improvement of positive symptoms after AMPT medication [2].

In conclusion, the current literature, although scarce, suggests that AMPT may have beneficial effects on dyskinesia, Huntington’s chorea, Tourette syndrome, mania, substance abuse, 22q11DS and psychosis. However, double-blind, placebo-controlled studies are lacking and are needed before firm conclusions can be drawn.

SAFETY ISSUES
Depletion of catecholamines can cause adverse effects of varying severity. The most common adverse reactions to acute AMPT administration are moderate to severe sedation, anxiety and EPS, all of which were described in the AMPT challenge section above.

Diarrhea is reported in up to 10% of subjects, but is not reported in most acute challenge studies [29,56,67,78]. Galactorrhea could be expected due to higher PRL levels in chronic use, but is not commonly reported. Engelman et al reported that one of 52 of chronic AMPT users patients experienced galactorrhoea [29]. Acute dystonia is also reported in 0-25% patients after AMPT challenge [2,35,56,62] or after AMPT withdrawal [52], and akathisia was reported in 0-60% of patients [35,90,97]. Crystalluria was reported in 0-66% of patients [2,52,88,90]. Animal studies have indicated that crystallization of AMPT in the urinary tract can be prevented by high fluid intake [45,70]. Bearing this in mind most studies recommended that patients drink at least 2 liters of fluid per day throughout the study, and urinary sediments were examined for crystals.
Some individual subjects may react dramatically to AMPT depletion, and experience a wide range of symptoms including obsessive-compulsive symptoms, thought disorders, and anxiety and depressive symptoms, highlighting the importance of the role of DA in major psychiatric disorders [24]. Steinsapir reported visual hallucinations and psychosis in one patient taking AMPT for at least 3 weeks at a dose of 1-2 grams per day as pre-operative treatment for pheochromocytoma [88]. One case report [17] described a patient with Huntington’s chorea who was treated with TBZ (350 mg per day) and AMPT (250 mg per day) for 7 months, who developed hyperpyrexia, hyperthermia and dystonia, consistent with a diagnosis of neuroleptic malignant syndrome (NMS), suggesting that not only DA receptor blockade but also (low dose) DA depletion can cause this potentially deadly condition.

When using AMPT therapeutically, obviously one should analyze if the benefits of the treatment outweigh the discomfort due to possible side effects. Side effects are always reported to be temporary, and disappear after the withdrawal of the AMPT medication. Apart from sedation, which is almost unanimously seen in patients, the different transient adverse effects can be totally absent in one study and quite common in others. The reason for this is unclear. It can be a result of the applied dose of AMPT, the regimen of administration, the length or methodology of the study. Common AMPT depletion procedures administer a total amount of 4500 – 8000 mg of AMPT in a 25 to 48 hour study period [10]. To the best of our knowledge, the relation between dose of AMPT and the occurrence of side effects has not been studies yet. Nevertheless there is evidence that high doses of AMPT cause some of the more severe symptoms [24], and that moderate weight-adjusted doses (40 mg AMPT per kilogram body weight) yield satisfactory DA depletion results [12,42]. Therefore, limiting the dose of AMPT as much as appropriate seems recommendable.

CONCLUSION
AMPT is increasingly popular as a means of depleting DA in human clinical research and provides an useful paradigm for elucidating the function of catecholaminergic pathways. Nevertheless the depletion methodology is time-consuming and produces variable dose-dependent relationships. Furthermore there have been no test-retest studies to our knowledge. As a therapeutic agent it has been approved to treat the consequences of phaeochromocytoma. In addition, beneficial effects have been studied in a range of other neuropsychiatric disorders and there is promising evidence of varying quality and persuasiveness that AMPT has some beneficial effects on dyskinesia, Huntington’s chorea, Tourette syndrome, mania, substance abuse, 22q11DS and psychosis. These results might warrant further research since controlled studies are mostly lacking. This is equally true with respect to the unclear dose-response relationship for side-effects. Severe adverse effects are rare, and side effects are transient and do not commonly cause subjects to withdraw from studies. Nevertheless discomfort due to higher doses of AMPT is common and it can be recommended to limit the dose of AMPT administered to subjects as much as appropriate.
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