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REVIEW

Tranylcypromine in mind (Part II): Review of clinical pharmacology and meta-analysis of controlled studies in depression

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Abstract
It has been over 50 years since a review has focused exclusively on the monoamine oxidase (MAO) inhibitor tranylcypromine (TCP). A new review has therefore been conducted for TCP in two parts which are written to be read preferably in close conjunction: part I - pharmacodynamics, pharmacokinetics, drug interactions, toxicology; and part II - clinical studies with meta-analysis of controlled studies in depression, practice of TCP treatment, place in therapy. The irreversible and nonselective MAO-A/B inhibitor TCP has been confirmed as an efficacious and safe antidepressant drug. For the first time, a meta-analysis of controlled clinical trials in depression demonstrated that TCP is superior to placebo (pooled logOR = 0.509, 95%CI = 0.026 to 0.993, 4 studies) and equal to other antidepressants (pooled logOR = 0.208, 95%CI = −0.128 to 0.544, 10 studies). In treatment resistant depression (TRD) after tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), TCP was superior to placebo (logOR = 2.826, 95%CI = 1.494 to 4.158, one study) and non-established antidepressants (pooled logOR = 1.976, 95%CI = 0.907 to 3.045, 4 studies), and was equal to other MAO inhibitors and an antidepressant combination (pooled logOR = −0.366, 95%CI = −0.869 to 0.137, 4 studies). Controlled studies revealed that TCP might provide a special advantage in the treatment of atypical depression, which was supported by a recent PET study of MAO-A activity in brain. However, TCP treatment remains beset with the need for a mandatory tyramine-restricted diet and is therefore limited to use as a third-line antidepressant according to recent treatment algorithms and guidelines for depression treatment. On the other hand, the effort needed to maintain a tyramine-restricted diet may have been overestimated in the perception

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of both doctors and patients, which may have led to relative underuse of TCP. Interaction with serotonergic drugs bears the risk of severe serotonin toxicity (SST) and combination with indirect sympathomimetic drugs may result in hypertensive crisis which both adds to the risks of TCP. At the same time, TCP has low to no risks of central anticholinergic, sedative, cardiac conduction, body weight, hemostatic effects, or pharmacokinetic drug interactions. Neuroprotection by MAO inhibitors due to reduced oxidative stress is becoming increasingly studied. Taken together, TCP is being increasingly recognized as an important option in systematic treatment approaches for patients suffering from severe courses of depression, such as TRD and atypical depression, by offering a MAO-related pathophysiological rationale.

1. Introduction

A general introduction to this review part II on tranylcypromine (TCP) has already been given in part I (pharmacology) of the joined reviews. Consecutively, the main data of the clinical pharmacology of TCP are presented here which includes, for the first time, a meta-analysis of controlled studies in depression. A discussion of the clinical practice of TCP treatment is added referring to special requirements of this irreversible monoamine oxidase (MAO)-A/B inhibitor. This is completed by an overview of the state of the art discussion in medical literature concerning the benefit-risk ratio and place in therapy of TCP.

2. Experimental procedures

The experimental procedures of the review have already been presented in part I.

For the meta-analysis, controlled studies of TCP monotherapy in depression have been identified from tabular compilations in two comprehensive reviews covering the periods before 1965 (Atkinson and Ditman, 1965) and before 1993 (Thase et al., 1995). Considering these studies in the previous reviews was regarded as a sufficient quality standard; however, no violations in minimal quality requirements for the target of this meta-analysis were detected in our own evaluation (prospective parallel or cross-over, open, single-blind or double-blind study, placebo or active drug comparator, only depressive patients, acute treatment, no antidepressant comedication, sufficient description, and minimum of 10 patients). Studies after 1993 were searched in MedLine using the search terms tranylcypromine and depression. Data of published study reports have been extracted and documented by one author (SU) and the file has been confirmed by another author (RR). Six studies were found that compared TCP with placebo (Bartholomew, 1962; Glick, 1964; Gottfries, 1963; Khanna et al., 1963; Himmelhoch et al., 1982; White et al., 1984) and 19 studies with active comparator: the TCAs imipramine (Freyhan, 1960; Himmelhoch et al., 1991; Spear et al., 1964; Thase et al., 1992a), amitriptyline (O'Brien et al., 1993; Razani et al., 1983; White et al., 1980a), imipramine and amitriptyline (Richmond and Roberts, 1964), and nortriptyline (White et al., 1984), the MAO inhibitors phenelzine (Birkenhäger et al., 2004; Glick, 1964), brofaromine (Nolen et al., 1993; Volz et al., 1994a, 1994b), and moclobemide (Heinze et al., 1993), the serotonin precursor L-5-hydroxytryptophan (Nolen et al., 1985), the dopamine and norepinephrine reuptake inhibitor nomifensine (Nolen et al., 1988), the combination of venlafaxine and mirtazapine (McGrath et al., 2006), and lamotrigine (Nolen et al., 2007). Eight studies were conducted between 1960 and 1964 (early studies). The remaining 17 studies all were conducted between 1980 and 2007 (late studies). Of the 25 studies, 17 were double-blind randomized trials, 5 early studies (62.5% of early studies) and 12 late studies (70.6% of late studies). One study was single-blind, 5 studies were open label, and 22 were randomized. Modern criteria of psychiatric diagnosis, such as Diagnostic and Statistical Manual of Mental Disorders (DSM III or IV) were used in the studies after 1980. Only 4 studies did not use a structured and validated rating scale, such as the Hamilton Depression Scale (HAMD). As these were early studies, this marks the only important difference between early and late studies. It is therefore concluded that the quality of studies was high for the 1536 patients included, with 664 patients receiving TCP (Tables 1, 2).

The effect size of studies was calculated as the log odds ratio (logOR) of the number of treatment responders and nonresponders in TCP and control group, which were categorized according to 50% HAMD improvement as a cut-off point in the majority of studies or according to a predefined level of Clinical Global Impression (CGI) improvement or similar in the remaining studies. A standard continuity correction of 0.5 was applied to one study that included nil cells. All patients randomized or later defined as drop-outs were included in the analysis (intention-to-treat sample; ITT). Drop-outs were set as nonresponders for studies lacking these detailed data. In three studies without ITT data, transformation of completer's data to ITT data according to the mean ratio of completer's and ITT data of the other studies was needed. The summary effect size was calculated as the pooled logOR according to a fixed effect model in a Microsoft Excel spreadsheet (D'Agostino and Weintraub, 1995; Neyeloff et al., 2012).

In the case of heterogeneity of studies, explorative sensitivity analyses were conducted with respect to subgroups of studies using treatment resistant depression (TRD) versus non-TRD in a first approach and pharmacological group of comparator drug as a second approach for group parameters to obtain homogeneous data sets. This resulted in four pooled odds ratios according to homogeneous data sets for TCP versus placebo in non-TRD, TCP versus comparator antidepressant in non-TRD, and two times for TCP versus comparator antidepressant in TRD according to two different drug groups.

3. Clinical studies and therapeutic experience with tranylcypromine

3.1. Meta-analysis of prospective controlled studies in depression

Meta-analyses of TCP in depression including formal statistical calculations of overall effect size (e.g., with pooled odds ratios), are currently lacking in the literature. Therefore, we conducted a meta-analysis to compare TCP with other antidepressants and placebo. Experimental