EFFECTIVENESS OF PAROXETINE IN THE TREATMENT OF DEPRESSION

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Abstract

Paroxetine is a potent and selective serotonin reuptake inhibitor (SSRI) with currently approved indications for the treatment of depression, obsessive-compulsive disorder, panic disorder and social phobia. It is also used in the treatment of generalized anxiety disorder, post traumatic stress disorder, premenstrual dysphoric disorder and chronic headache. Paroxetine, a phenyl piperidine derivative, is the most potent inhibitor of the reuptake of serotonin (5-hydroxytryptamine, 5-HT) of all the currently available antidepressants including the class of SSRIs. It is a very weak inhibitor of nor-epinephrine (NE) uptake but it is still more potent at this site than the other SSRIs. One of the top SSRIs in terms of nor-epinephrine to serotonin (NE5-HT) absorption inhibitory inhibition selectivity is paroxetine. Comparatively to tricyclic antidepressants (TCAs), paroxetine has a lower propensity to have adverse effects on the central and autonomic nervous systems since it has limited affinity for the catecholaminergic, dopaminergic, or histaminergic systems. Compared to TCAs, paroxetine has substantially lower muscarinic cholinergic receptor affinity. Additionally, paroxetine causes adaptive alterations in somatodendritic (5-HT1A) and terminal (5-HT1B1D) autoreceptors that are distinct from those caused by TCAs. It also inhibits nitric oxide synthase. It is a cytochrome isoenzyme P450 2D6 substrate as well as an inhibitor. The first pass metabolism of paroxetine is substantial and partially saturable when taken orally.Its metabolites are inactive pharmacologically in vivo. After 4 to 14 days, steady state levels are attained, and a half-life of 21 hours for elimination is consistent with once-daily dosing. Adults, children, and the elderly all exhibit significant inter-individual variation in the pharmacokinetics of paroxetine, with the latter showing higher plasma concentrations and slower clearance. Severe renal and hepatic dysfunction also results in decreased elimination. Even in overdose, however, serious adverse outcomes are quite uncommon. Overall, paroxetine is safe and effective for treating both anxiety and depressive disorders across the age spectrum.

Keywords: Anxiety—Depression—Obsessive-compulsive disorder—Panic disorder—Paroxetine—Serotonin reuptake inhibitors—Social phobia.

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1. Introduction:

Both under diagnosis and under treatment of depression are common. Only approximately 70% of individuals will show an acceptable response to antidepressant drug therapy with remission from their depression, even with treatment. In addition, many patients only experience partial remission and will eventually relapse. Untreated depression has significant personal and societal costs. Compliance is important for effective therapy. Ineffective treatment or no treatment at all, which would have a detrimental effect on recovery, could result from poor adherence to what is anticipated to be a long-term treatment. There is evidence that side effects are connected to lower compliance.[2].Obsessive compulsive disorder (OCD), panic disorder, social phobia, and other conditions that all exhibit some response to antidepressant medications have all been the focus of active research projects since the late 1970s. Paroxetine is an antidepressant resulting from such rational drug development. It is a potent and selective SSRI, which is approved for the treatment of depression worldwide. It demonstrates a broad spectrum of efficacy and it has also been approved for the treatment of OCD, panic disorder and social phobia in different countries.[3,6] Treatment of generalised anxiety disorder (GAD) and post-traumatic stress disorder are potential future indications (PTSD). Paroxetine has recently finished clinical studies treating premenstrual dysphoric disorder (PMDD). Additionally, it has been used to treat chronic headaches, vasovagal syncope, and diabetic neuropathy. Due to the elimination half-life of paroxetine, once-daily dosing is possible. It has a low toxicity in an overdose and is well tolerated in certain populations, such as the elderly. It also has a positive side effect profile.[12,13]

Chemistry And Biochemical Mechanism of Action

Traditionally, the classification of antidepressant drugs has been based either upon chemical structure, e.g., the TCAs, or mechanism of action e.g., the monoamine oxidase inhibitors (MAOIs).[5] Paroxetine is functionally classified as a selective serotonin reuptake inhibitor, a class of structurally unrelated drugs which enhances serotonergic transmission by blocking the presynaptic active membrane transport mechanism for the reuptake of serotonin and consequently increases serotonergic activity at the post synaptic receptor.

Paroxetine's affinity for the serotonin receptor is 2 to 3 orders of magnitude greater than the Km of serotonin and as with the other members of the class, it effectively increases the concentration of endogenous serotonin in the synaptic cleft.[4] It is highly lipophilic. The structure of paroxetine, a phenylpiperidine derivative, is shown in Fig. 1.

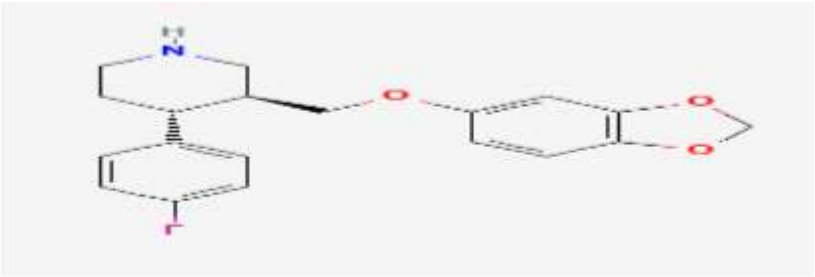

Fig 1: Chemical Structure of Paroxitine

Antidepressant medications have not yet been linked to a precise mechanism of action for treating depression. There is a wide range of potencies for nor-

epinephrine (NE), serotonin (5-HT), or dopamine (DA) reuptake inhibition in currently marketed medications. Although the cause and pathophysiology of depression are still unknown, there is strong evidence that the 5-HT and NE systems are implicated in its pathogenesis, and medications that target these two systems have proved effective in treating depressed disorders. Paroxetine is the most potent inhibitor of 5-HT reuptake of all currently available antidepressants. It is a very weak inhibitor of nor-epinephrine uptake but it is still more potent at this site than the other SSRIs and this may contribute to its efficacy at higher doses. Paroxetine has some of the best SSRI selectivity, measured by the ratio of inhibition of NE to 5-HT uptake (NE-5-HT). For any other receptors, it has a minimal affinity.[14] When compared to TCAs, paroxetine does not cause the same secondary adaptive receptor alterations over time. In contrast to TCAs, which sensitise postsynaptic 5-HT1A receptors, long-term use of paroxetine (around two to three weeks) results in a larger release of serotonin with each action potential by reducing the responsiveness of somatodentritic (5-HT1A) and terminal (5-HT1B1D) autoreceptors. Regarding the therapeutic benefits of paroxetine, these adaptative alterations in synaptic serotonergic receptors are probably significant.[11]

Preclinical Pharmacology

Actions on Neurotransmitter Reuptake

In vitro studies in rat brain synaptosomes have shown paroxetine to possess the most potent inhibition of 5-HT reuptake of the SSRIs , as summarized in Table 1. Since the main metabolites produced after oral administration of paroxetine have minimal activity, they do not modify the pharmacological profile of the parent compound and it is unlikely they contribute to its clinical effects.[10] The blockade of serotonin reuptake by paroxetine is prolonged and maintained upon repeated administration . From in vitro and ex vivo studies, the blockade of serotonin reuptake into synaptosomes is dose dependent . In vivo micro dialysis experiments show that the acute administration of paroxetine at doses of 5 mg/kg increases extracellular serotonin levels .

The results of in vitro and in vivo studies have shown that much higher concentrations of paroxetine are required to inhibit the reuptake of NE and DA . Although the concentration of paroxetine necessary to inhibit NE uptake is lower than the concentrations of any other SSRIs required to achieve the same effect, as a result of its potency in 5-HT reuptake inhibition, paroxetine's selectivity (NE/5-HT) is second only to that of citalopram.[18]

Effects of Repeated Administration of Paroxetine on Receptor Sensitivity

Although the inhibition of serotonin uptake occurs within hours of drug ingestion, theclinical response in psychiatric disorders such as depression represents a more delayedprocess, usually taking at least 2 weeks or more. This may be due to the time required forthe drugs to exert their full effects through a reaction cascade following drug intake.[15]

TABLE 1. In vitro binding profiles from rat brain tissue synaptosomesa

Compound	5-HT	NE	DA
Paroxetine	**1.1**	**350**	**2000**
Fluvoxamine	**6.2**	**1100**	**>10,000**
Fluoxetin	**25**	**500**	**4200**

Pharmacokinetic Properties

High-performance liquid chromatography is capable of measuring paroxetine in human plasma with accuracy (HPLC) The pharmacokinetics of paroxetine have a high degree of inter-individual heterogeneity. Table 2 lists the paroxetine pharmacokinetic parameters at single dosages of 20 to 50 mg. There is no evidence that efficacy of paroxetine correlates with its plasma concentrations, given the relatively flat dose–response curve for the antidepressant effect of paroxetineat the dose range of 20 to 40 mg/day (the dose generally used in correlation studies).The pharmacokinetics of paroxetine in depressed patients without renal or hepatic dysfunction, is similar to that in healthy volunteers.[17]

TABLE 2. Pharmacokinetic parameters (mean values) of paroxetine in healthy volunteers after oral administration of single dose of paroxetine over the range 20–50 mga

	Dose (mg)		
Parameters	**20**	**30**	**40**
Cmax (ng/ml)	10.7	17.6	31.1
Cmin (ng/ml)	5.1	8.5	11.7
tmax (h)	5.8	6.3	5.5
t1/2 (h)	21.1	21.7	17.4
AUC (ng h/ml)	454	797	763

Clinical Studies

Depression:

Depression is a disabling illness and, given its high prevalence, it has a marked impact on occupational and social functioning.[16,17] It is associated with significant morbidity and mortality . Untreated or suboptimally treated depressed patients have an increased risk of suicide attempts, longer periods of disability and increased rates of hospitalization . Clinical trials have compared paroxetine to placebo, imipramine, clomipramine, amitriptyline, dothiepin, doxepin ,lofepramine, maprotiline, and mianserin . Paroxetine has also been campared in review articles with other SSRIs, including fluoxetine, fluvoxamine, and sertraline nefazodone , as well as electroconvulsive therapy (ECT) .Equivalent efficacy of paroxetine, fluoxetine, fluvoxamine and sertraline has also been demonstrated in randomized, parallel, double-blind clinical trials . One study suggested that paroxetine has a more rapid onset of action and may be more effective in relieving associated anxiety than fluoxetine , although the differences in the onset ofaction and in anxiolytic activity were not confirmed in another study . No significant differences between paroxetine to fluvoxamine were reported in two other studies .The only study comparing paroxetine and sertraline involved hospitalized patients withdelusional depression; no significant differences between the two drugs were found in patients who completed the trial .

In a randomized double-blind clinical trial the efficacy of paroxetine was found to be equivalent to that of nefazodone.[12]

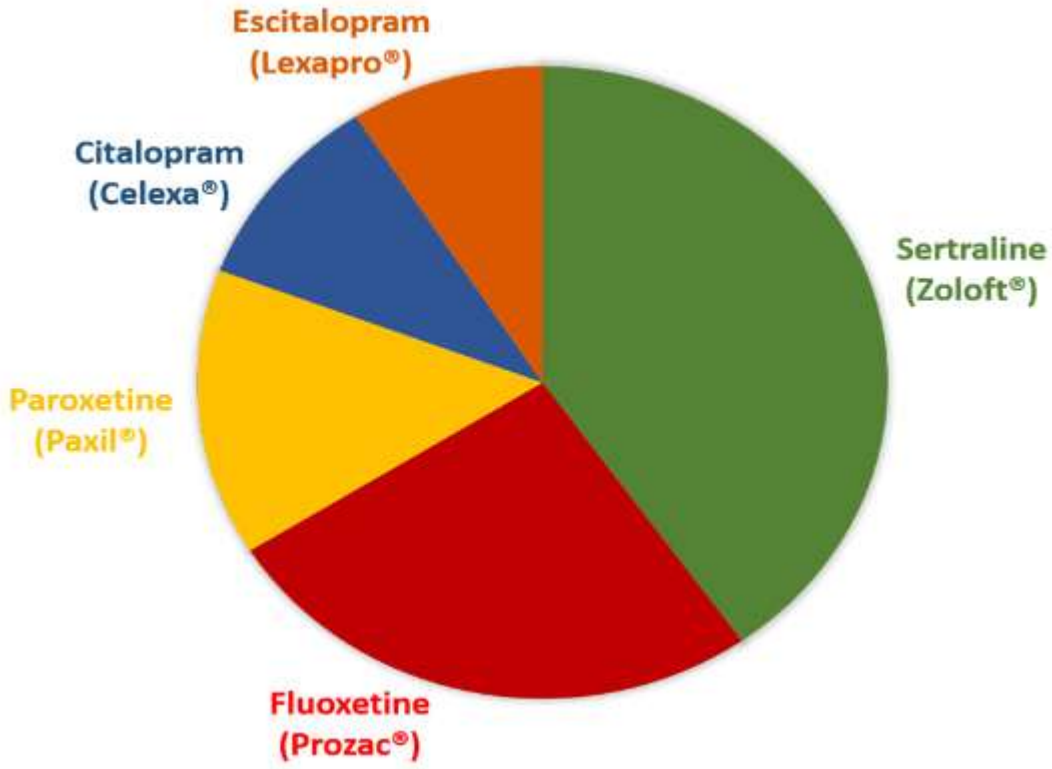

Fig 2 : Depression Treatment

Obsessive-Compulsive Disorder

The chronic and incapacitating condition known as obsessive-compulsive disorder (OCD). Estimates place its lifetime prevalence between 2 and 4%. Up to 80% of OCD cases see an early onset during infancy or adolescence.[16]. There is evidence that clomipramine improvesOCD independently of its antidepressant properties implying potential serotonergicinvolvement in the pathogenesis of OCD. In patients with OCD, paroxetine at a dose of 20 to 60 mg/day, significantly reduced the scores on the Yale-Brown Obsessive-CompulsiveScale and the National Institute of Health Obsessive-Compulsive Scale comparedtoplacebo . Response to paroxetine was apparent after 2 weeks and more significant after 6 weeks. Its efficacy was maintained for up to 12 weeks. In these studies, paroxetine, 20 to 60 mg/day, appeared to be at least as efficacious as clomipramine, 50 to 250 mg/day[14].

Treatment of OCD

Paroxetine should be used as a single morning dose of 10 mg/day for the treatment of OCD, with weekly dose increases of 10 mg up to a maximum of 60 mg/day advised. For adults, the typical effective dose is 40 mg per day. Given that its effectiveness is equivalent to that of clomipramine but that it is substantially better tolerated—the dropout rate associated with adverse events in studies was significantly lower—paroxetine appears to be a first-line treatment for OCD.[12] 9% for paroxetine (not different from placebo)compared to 17% for clomipramine. Overall paroxetine treatment led to fewer prematurewithdrawals than with either clomipramine or placebo . Further clinical trials comparing paroxetine to TCAs and to other SSRIs with long term evaluation

of efficacy areneeded as well as studies in younger patients in the 8 to 17 years range since the prognosisfor OCD is likely to be improved if early treatment is initiated [13,18]

Panic Disorder

Panic disorder is an incapacitating condition with long term negative consequences. Lifetime prevalence is estimated between 1.5 and 3% and may be up to more than 15%. TCAs, MAOIs, and high potency benzodiazepines have all been used in the treatment of panic disorder. The efficacy of these drugs is established but all of them have significant drawbacks related to tolerability, dependence potential, complexity of daily regimen and toxicity in overdose.

In patients with panic disorder with or without agoraphobia, paroxetine, 10 to 60 mg/day, significantly reduced the frequency of panic attacks and led to greater improvementin generalized anxiety and phobic avoidance[11]. The patients in this placebo-controlledstudy were evaluated by various scales including the Marks Sheehan Phobia,Sheehan Disability, Hamilton Anxiety Rating, CGI, Montgomery–Asberg DepressionRating, Zung Self Rating for Anxiety, and Patient Global Evaluation Scales[9]. Responseto paroxetine was evident after 3 to 4 weeks and its efficacy in reducing panic attack frequencywas maintained for up to 48 weeks. Treated patients continued to show improvementand demonstrated a lower risk of relapse . Compared to clomipramine atdoses of 10 to 150 mg/day, paroxetine at doses of 10 to 60 mg/day, was at least as efficaciousin reducing the frequency of panic attacks and relieving associated symptoms suchas anxiety, phobia, family, social life, and work problems [19]Paroxetine was significantlymore effective than clomipramine with respect to the percentage of patients whohad no panic attacks at all between weeks 7 and 9 of treatment (end point of study). Paroxetinehad also a more rapid onset of action than clomipramine (4 to 5 weeks with paroxetinecompared to 10 to 12 weeks with clomipramine) and greater efficacy than placebo.

In the treatment of panic disorder, with or without agoraphobia, it is recommended tostart paroxetine at a single morning dose of 10 mg, and to increase the dose by 10 mg/dayon a weekly basis to a maximum of 60 mg/day (usual effective dose is 40 mg/day).After 6 to 12 months of treatment, an attempt to taper and to discontinue the drug issuggested. If the patient experiences relapse, the treatment should be reinitiated and con-sideration given to indefinite maintenance therapy in situations of recurrent relapse[22] Of the currently available drugs for treating panic disorder, SSRIs appear to be more efficaciousand better tolerated. Paroxetine is, therefore, a possible rational first-line choicefor short term treatment of panic disorder as well as its long-term management[14] Further clinical trials comparing paroxetine to benzodiazepines, such as alprazolam, MAOIs and other SSRIs, may be helpful in the future.

Adverse Effects and Tolerability

In the treatment of depression, avoiding particular side effects is an important determining factor influencing the choice of antidepressant. Some side effects may pose serious risks for the health of the patient, e.g., cardiac arrhythmia while others may interfere with daily activities, e.g., driving. Side effects impact negatively on compliance and potentially response to treatment.

Knowledge of drug–drug interactions may also be clinically very important and a summary of reported and potential drug interactions, that can occur with paroxetine, is provided in Table 3.

Paroxetine's side effect profile in terms of the nature and incidence of adverse events,is similar in patients treated for depression, GAD, panic disorder, OCD and social phobia,e.g., in GAD, patients

receiving paroxetine at a dose of 20 mg/day, did not show any significantdifference in premature study terminations due to adverse effects than patientstreated with diazepam[10] Although nausea was more frequent with paroxetine anddrowsiness more frequent with diazepam; in comparison with imipramine, paroxetine patientsexperienced fewer side effects, like constipation, drowsiness and dry mouth, all ofwhich being more frequent with the TCA.

Overall, there were no more treatment dropoutsrelated to adverse events in paroxetine treated patients than in patients receiving placebo(around 10%) and dizziness, constipation and somnolence incidences were similar in bothgroups. Side effects tended to diminish after the first week of treatment and dry mouth wasmore frequently reported with paroxetine at doses of 40 mg/day compared to doses of 20 mg/day and placebo.

TABLE 3. Reported and potential drug interactions with paroxetine

Increased adverse events
❖ Antidepressants (desipramine, imipramine, nortriptyline, amitriptyline, trimipramine)
❖ Antipsychotics (phenothiazines, clozapine, molindone, haloperidol, pimozide)
❖ Anticonvulsants (phenytoin)
❖ Type 1c antiarrhythmics (propafenone, flecainide)
❖ Anticholinergics (benztropine, procyclidine)
❖ Xanthines (theophylline)
Potentiated serotonergic activity
➢ MAOIs
➢ Moclobemide
➢ Trazodone, nefazodone
➢ Lithium
➢ Tryptophan
➢ OTC cold preparations

Other Uncommon Side Effects

Concerns with use of paroxetine include not only increased thoughts of aggression or suicide but also hypomanic/manic mood, abnormal dreams, rash, muscle pain, muscle weakness, electric shooting sensations, heart palpitations, feeling flushed, tingling sensations, and fasciculations[11,18]. Again, the 2004 FDA black box warning eventually placed on all antidepressants indicated a two-fold increase in suicidal ideation and

aggression in patients under the age of 24, especially in adolescents and children. On December 22, 2006, a U.S. court decided in Hoorman et al. v. SmithKline Beecham Corporation that individuals who purchased Paxil or Paxil CR (paroxetine) for a minor child possibly were eligible for benefits under a $63.8 million Proposed Settlement. The lawsuit won the claim that GlaxoSmithKline promoted Paxil and Paxil CR for prescription to children and adolescents while withholding and concealing material information about the medication's safety and effectiveness for minors [16].

Discontinuation Syndrome

As with other antidepressants, suddenly stopping paroxetine can lead to a discontinuation syndrome characterized by feelings of sickness, diaphoresis, asthenia, myalgia, parasthesias, fatigue, electric shock sensations, depression (including suicidality), anxiety, insomnia, headache, chills, stomachache, nausea, vomiting and diarrhea. Step-wise dose reduction involving slowly tapering down the drug over a period of at least two weeks is recommended for both discontinuation and cross tapering with another antidepressant [15]

2. Conclusions

Paroxetine is an effective antidepressant which also has proven effective in treating generalized anxiety, panic, posttraumatic stress, social phobia, premenstrual dysphoric disorder, and obsessive-compulsive spectrum disorders . It also is being used to treat peri-menopausal or menopausal hot flashes. Currently, it has received FDA indications for major depressive disorder, social phobia, generalized anxiety disorder and hot flashes. A review of the literature, however, indicates that paroxetine has serious side and adverse drug effects ranging from congenital birth defects and heart abnormalities to breast and other possible cancers. It also may, along with other SSRIs and SNRIs, increase suicidality, aggression and akathisia in pediatric patients with incidence outcomes which initially may have been significantly underestimated in clinical trials. Women with a family history of breast cancer should only be initiated or maintained on paroxetine therapy when effective treatment cannot be rendered by other SSRIs, another class of antidepressants or anxiolytics, electroconvulsive therapy, or somatic treatments.

Overall, nevertheless, paroxetine's issues and hazards seem to make it the least risky of all SSRIs and SNRIs, and if not for the low therapeutic indices of TCAs and MAOIs, potential cardiotoxicity, and elevated risk of serotonin syndrome, the least risky of all antidepressants. These findings should prompt medical professionals to recommend, begin, and continue paroxetine treatment with much greater caution in women than they would with other antidepressants.

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