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Review article

NK1 receptor antagonists for depression: Why a validated concept was abandoned

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ABSTRACT

Background: NK1 receptor antagonists were abandoned despite antidepressant efficacy in five randomized clinical trials. The loss of confidence may be attributed to the failure of a Phase III clinical program with the NK1 receptor antagonist aprepitant in Major Depression. This review examines how PET receptor occupancy was used to select doses for aprepitant and that these may not have achieved adequate exposure.

Methods: PubMed, Google Scholar, and FDA databases were searched for articles concerning NK1 receptor antagonists, human PET receptor occupancy and clinical trials in Major Depression.

Results: Antidepressant efficacy was initially demonstrated with three NK1 receptor antagonists, including aprepitant. A nanoparticle formulation of aprepitant was then developed to improve oral bioavailability. In PET studies, doses of 80 and 160 mg achieved a high level (~ 90%) of occupancy of NK1 receptors in the human brain and were selected for Phase III. The efficacy of these doses of the nanoparticle formulation may not have been established in depressed patients prior to Phase III, and previous formulations required a dose of 300 mg of aprepitant for efficacy. No antidepressant effect of 80 or 160 mg of aprepitant was found, and it was concluded that the NK1 antagonist concept was flawed. However, subsequent studies with other compounds showed that a higher level of NK1 receptor occupancy (100%) was required for antidepressant efficacy.

Limitations: Key data concerning the bioequivalence of different formulations of aprepitant have not been published. The importance of NK1 antagonists for pharmacotherapy of depression and other psychiatric disorders has not been established in clinical practice.

Conclusion: Aprepitant may have failed in Phase III because of an inadequate understanding of the relationship between brain NK1 receptor occupancy and clinical response. A validated and novel mechanistic approach to treat depression has been misperceived as ineffective and abandoned. Caution should be exercised in the appropriate use of PET occupancy data to select doses for drug development programs in neuropsychiatry. The relationship between exposure, receptor occupancy and clinical response should be established. A crisis of confidence has followed the failure of this and other programs in neuropsychiatry, with a far reaching and detrimental impact on pharmaceutical research.

1. Introduction

Antidepressant drug development has remained stagnated for many decades and is now generally viewed as too high risk to warrant investment (Wegener and Rujescu, 2013). Constraints on the design of clinical registration studies have effectively handicapped the ability of drug makers to generate convincing efficacy data with antidepressants. These include a requirement to demonstrate superior efficacy over placebo using the Hamilton Depression rating scale that provides only a small margin of differential response (around 2–4 points) and has poor assay sensitivity. An active comparator arm is needed to discriminate a true negative trial that had assay sensitivity from a failed trial that did not. In addition, the need to establish a minimally effective dose demands study designs with multiple treatment arms that further diminishes the signal to noise ratio (Khan and Brown, 2015). For these reasons it has not been possible to establish a clear dose-response relationship for most antidepressants. Since the serendipitous discovery of tricyclic antidepressants in the 1950s, most approved antidepressants share a common mechanism of action: serotonin or noradrenaline reuptake inhibition. Given the high risks associated with drug

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development, it is not surprising that the field is dominated by a single mechanistic class of monoaminergic antidepressants for which the risk of failure was mitigated by the precedent of prior 'me too' drug approvals.

In 1998, Merck announced a groundbreaking discovery of the first new mechanism to treat major depression for over 4 decades (Kramer et al., 1998). The target was the tachykinin NK1 receptor and its endogenous neurotransmitter Substance P. The neuropeptide and its receptor are expressed in high density in brain regions that are associated with neurochemical and physiological responses to stress, notably the amygdala and associated output pathways to the thalamus and hypothalamus (Rupniak, 2002). Substance P and NK1 receptors also have intimate neuroanatomical associations and functional interactions with serotonergic and noradrenergic pathways that are the targets of monoaminergic antidepressant drugs (Conley et al., 2002; Maubach et al., 2002). NK1 receptor blockade or genetic deletion causes an increase in hippocampal neurogenesis that is a characteristic feature of antidepressant therapies (Morcuende et al., 2003; van der Hart et al., 2005). No less than five clinical trials with different compounds conducted by Merck, Pfizer and GSK confirmed the clinical efficacy of NK1 receptor antagonists in studies that recruited over 1300 patients with major depression; this represented a substantial effort by several pharmaceutical companies that were committed to finding an innovative, non-monoaminergic therapy for depression. Despite the independent replications with structurally distinct molecules and a compelling body of preclinical data underpinning the mechanism of action, in 2003 the failure of a large Phase III depression program led to a declaration that the concept was flawed, and the field was subsequently abandoned.

The NK1 antagonist program had high visibility and prominence because of the need to develop novel therapies for patients who either do not respond adequately to monoaminergic antidepressants, or are intolerant of them. Its collapse was followed by deep cuts in psychiatry research by the major pharmaceutical companies. There are valid concerns that drug development in psychiatry is 'too difficult', that animal models are unpredictive of human disease, and that rating scales needed for registration studies are insensitive measures of clinical response. Since the NK1 antagonist program remains a well validated and mechanistically distinct approach to treat depression, it is important to understand what went wrong and consider the implications of new information published since the field was abandoned.

2. Methods

PubMed and Google Scholar were searched for articles concerning NK1 receptor antagonists, human NK1 receptor occupancy studies, and clinical trials in Major Depression. Information regarding the pharmacokinetics, metabolism and formulation of aprepitant was obtained from the NDA for Emend and from published articles.

3. Results

The difficulties of the NK1 antagonist program can be traced back to the decision to make a public announcement to shareholders that Merck was leading 'a breakthrough discovery' in psychiatry soon after the results of the first proof of concept study with aprepitant (MK-0869) were known, a story that made headline news (Langreth, 1998). Although the finding was confirmed in subsequent clinical trials, such an early and strident public declaration would prove problematic because the study had not yet been formally replicated, and depression is well known for the high rate of clinical trial failures even with established drugs. Any public announcement promising a medical revolution in the absence a balanced consideration of the risks inevitably results in unrealistic commercial expectations. Moreover, most major pharmaceutical companies had their own NK1 antagonist programs and were able to quickly switch their clinical focus to depression at a time when the innovator's own program was still at an early stage. Intense competition is counterproductive when seeking a depression indication since a race to be first to market conflicts with best practice to avoid study failure, notably the critical need to carefully select study sites and patients, and avoid pressured enrollment into clinical trials (Mancini et al., 2014).

Before proceeding to Phase III development, the minimum effective dose of aprepitant had to be established in depressed patients. A six arm dose ranging study examining 10, 30, 100 and 300 mg of a new formulation of aprepitant versus 20 mg fluoxetine or placebo was conducted, but the results were uninformative since neither aprepitant nor fluoxetine differed from placebo at any dose tested (Kramer, 2000, 2001). Post-hoc analysis revealed a robust signal with fluoxetine and the highest dose of aprepitant (300 mg) in a subset of patients with severe depression (baseline HAMD17 scores $\geq$ 26), consistent with observations made using the first approved antidepressant, imipramine, in severely depressed patients (Klerman and Cole, 1965). Although aprepitant had generated positive findings in a landmark proof of concept study, its pharmacokinetic and metabolic profile included many undesirable features for an oral, centrally acting drug to be administered chronically. Aprepitant had poor oral bioavailability attributed to its insolubility and limited absorption, and there was a marked effect of food on plasma drug levels; it was primarily metabolized by CYP3A4, an enzyme with which it interacted in a complex manner over time, being first an inhibitor and then inducer of its own metabolism; it was highly bound to plasma protein ($>$ 99.9%), meaning that only a small fraction of free drug was available to interact with the target receptor; and finally aprepitant was a substrate of P-glycoprotein, an active transport mechanism that extrudes drugs from the central nervous system at the blood brain barrier (Sanchez et al., 2004; Shadle et al., 2004; Emend NDA, 2002). A compound free of such limitations would be a more attractive first choice therapy. Moreover, the synthesis of aprepitant was considered too inefficient and expensive to permit commercial scale-up since it employed toxic chemicals, cryogenic reactions, and generated such large quantities of waste as to be potentially harmful to the environment (Hargreaves et al., 2011). Such issues are particularly problematic when the drug is to be administered chronically and at a high dose. The company discontinued development of aprepitant for depression and switched to a more potent compound, L-759,274.

The L-759,274 program was not without its own challenges. First, a four arm dose range finding study with L-759,274 (needed to set doses for Phase III) was uninformative (an assay insensitive trial). However, in a two arm study conducted in patients with severe melancholic depression, a significant antidepressant effect of L-759,274 was observed versus placebo (Kramer et al., 2004). The patient populations in the positive studies with aprepitant and L-759,274 were similar, apart from a requirement for diagnosis of the melancholic subtype of Major Depressive Disorder for L-759,274 (i.e. various combinations of depression that was subjectively different from grief or loss; severe weight loss or loss of appetite; psychomotor agitation or retardation; early morning awakening; excessive guilt; and diurnal variation of mood). It is not known how many patients in the aprepitant study met a diagnosis of melancholia. Soon after replicating the antidepressant efficacy of aprepitant with the preferred compound, an unexpected and major setback resulted in the termination of L-759,274. As these frustrating delays stalled the innovator's program, a competitor gained ground. In 2002, Pfizer presented results from a four arm Phase II study in which their NK1 antagonist CP-122,721 (30 mg b.i.d.) and the SSRI fluoxetine (20 mg) showed a 12–13 point reduction in HAMD score from baseline, compared with 7.5 points for placebo, a statistically and clinically significant difference. Importantly, a smaller (nonsignificant) effect was seen at a lower dose of 10 mg b.i.d. of CP-122,721, indicating dose-related antidepressant efficacy and defining the minimally effective dose for further development (Chappell, 2002; McLean, 2005). The need to establish the minimally effective dose is a particularly challenging regulatory requirement in this patient population, and so was