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Personalized medicine in panic disorder: where are we now? A meta-regression analysis

Daniela Caldirola [a,*], Massimiliano Grassi [a], Alessandra Alciati [a], Alice Riva [a], Erika Sangiorgio [a], Silvia Daccò [a], Giampaolo Perna [a,b,c]

[a] Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, FoRiPsi, Via Roma 16, 22032, Albese con Cassano, Como, Italy
[b] Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, University of Miami, Miami, USA
[c] Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, University of Maastricht, Maastricht, The Netherlands

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ABSTRACT

Personalized medicine assumes that individual's unique characteristics are central in tailoring effective pharmacological interventions. The identification of predictors of pharmacotherapy effectiveness is crucial in panic disorder (PD), but consensus on this topic is still lacking. Consequently, we carried out a meta-analysis, according to PRISMA guidelines, with the aim of identifying sociodemographic and clinical moderators of short-term outcomes and tolerability of US FDA-approved medications for PD. We performed a database search on randomized placebo-controlled trials using PubMed, PsycINFO, and Embase. Through the selection process, we finally meta-analyzed 29 comparisons between paroxetine, venlafaxine XR or alprazolam and placebo. We employed the random-effects meta-regression technique. The major results were that longer illness duration was significantly associated with a lower rate of patients free from panic attacks at the end of trials with venlafaxine XR, and that higher age at the beginning of trials was significantly associated with a higher rate of dropouts because of side effects during trials with paroxetine. In addition, longer treatment was associated with a higher rate of patients free from panic attacks at endpoint in trials with venlafaxine XR. Overall, we found limited support for the moderating effects of sociodemographic and clinical variables on the short-term pharmacotherapy for PD. However, our results should be considered with caution considering the limited statistical power and the risk of publication bias. Future studies are needed to overcome the paucity of available data and the shortcoming of the current pharmacological studies in PD.

Introduction

The major goal of a personalized approach is to tailor interventions according to each patient's unique profile and characteristics. Although personalized medicine has already achieved successful results in several medical fields, such as oncology, its application in psychiatry is still limited [1]. The high variability in clinical outcomes/side effects of pharmacotherapy [2], as well as and in risk of relapse [3], among patients with the same psychiatric disorder is a challenging issue for clinicians. A personalized approach, based on reliable predictors of pharmacotherapy course, may provide relevant advances in the treatment of psychiatric disorders. Panic Disorder (PD), a common (lifetime prevalence is 3%–4%) and debilitating psychiatric condition [4], could greatly benefit from such an approach, because from a clinical perspective there is still a strong unmet need for more efficacious pharmacological interventions in this disorder. Several medications are effective for treating PD, including selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and benzodiazepines. Among these, SSRIs and the SNRI venlafaxine are considered first-line treatment agents because of their efficacy and favorable side-effect profiles [5–8]. Despite these pharmacological options, the clinical outcomes are often unsatisfying. In short-term clinical trials, 17%–64% participants with PD did not respond adequately to pharmacotherapy and continued to have PAs and/or maladaptive changes in behavior related to Panic Attacks (PAs) [9]. Recommended drugs do not achieve full remission in 20%–40% patients and additional cognitive behavioral therapy does not fill this gap. The rate of relapses within 6 months of drug discontinuation is 25%–50%, the rate of residual panic–phobic symptoms is up to 50%, and up to 30%

* Corresponding author at: Hermanas Hospitalarias - Villa San Benedetto Menni Hospital, FoRiPsi, Department of Clinical Neurosciences, via Roma 16, 22032, Albese con Cassano, Como, Italy.
E-mail address: caldiroladaniela@gmail.com (D. Caldirola).

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patients discontinue treatments because of side effects [8,10,11]. Currently, alternative strategies for optimizing outcomes of pharmacotherapy in PD are not achievable. Indeed, novel mechanism-based antipanic drugs are far from being implemented in clinical use [12], and no evidence supports the use of existing medications already approved for other psychiatric disorders in PD, such as second-generation antipsychotics [13].

The personalized approach to pharmacotherapy for PD, although at an early stage, appears to be the most promising way for increasing, within a reasonable time frame, the rate of successful outcomes in this disorder, similar to trends in other fields of medicine [14,15]. This strategy aims to tailor drugs to maximize therapeutic efficacy and minimize side effects according to each patient's unique characteristics. Personalized treatments may be carried out by identifying evidence-based predictors of treatment response and tolerability, to select those patients who may mostly benefit from a specific treatment [16]. Predictors can include both "clinical" variables easily measurable with clinical interviews and examinations, such as clinical features of the disorder, comorbidity, familiarity, gender, sociodemographic characteristics, and "biological" variables measurable with additional and more complex testing, such as neurobiological functions, biomarkers, and genetic/pharmacogenetic characteristics. As we reviewed elsewhere [17,18], only limited investigations have explored biological predictors of pharmacotherapy outcome in PD, which are not sufficient to provide reliable results. Instead, literature suggested that socio-demographic and clinical factors may be associated with the pharmacological response to different medications in both anxiety and depressive disorders [19–22]. In PD, several studies have examined potential clinical predictors of response to different pharmacotherapies, including clinical severity of the disorder, sociodemographic characteristics, gender, cognitive/psychological features, level of improvement in the first few weeks of treatment, and comorbidity with depressive symptoms/disorder or with personality characteristics/disorders [6,23–36]. However, the results are mixed and a reliable consensus is still lacking regarding which clinical predictors, if any, are worthy of being considered by clinicians when they prescribe medications for PD. To the best of our knowledge, no published meta-analyses had the primary aim of providing a quantitative review of these inconsistent data. To fill this gap, we carried out a meta-analysis on this topic, with the aim of identifying sociodemographic and clinical moderators of outcome and tolerability in the pharmacotherapy for PD. In the event of significant results, these variables could be used by clinicians as useful predictive tools of the antipanic treatment course. The meta-analytic method allows us to compare effect-sizes and assess for heterogeneity across studies, evaluating possible moderator effects. We only included randomized-controlled trials (RCTs) that can control for unspecific effects, such as placebo and/or expectation effects, spontaneous remissions, or differences in measurement. As we recently reviewed [18], the number of long-term trials in PD was very limited and did not allow us to perform a meta-analysis of the data. Thus, we included only short-term trials (i.e., 6–12 weeks). We included only medications that had been approved for PD by the US Food and Drug Administration (FDA), i.e., the SSRIs paroxetine, fluoxetine, and sertraline, the SNRI venlafaxine extended-release (XR), and the benzodiazepines alprazolam and clonazepam [37]. Finally, given that PD is a complex disorder, resulting from an interplay of unexpected panic attacks (PAs) and other heterogeneous psychopathological phenomena (i.e., anticipatory anxiety and maladaptive changes in behavior related to PAs), which probably involve distinct neural circuits [38,39], we focused, as clinical outcome, on PAs, which are hallmarks of PD.

Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [40]. The protocol for this meta-analysis has not been previously registered.

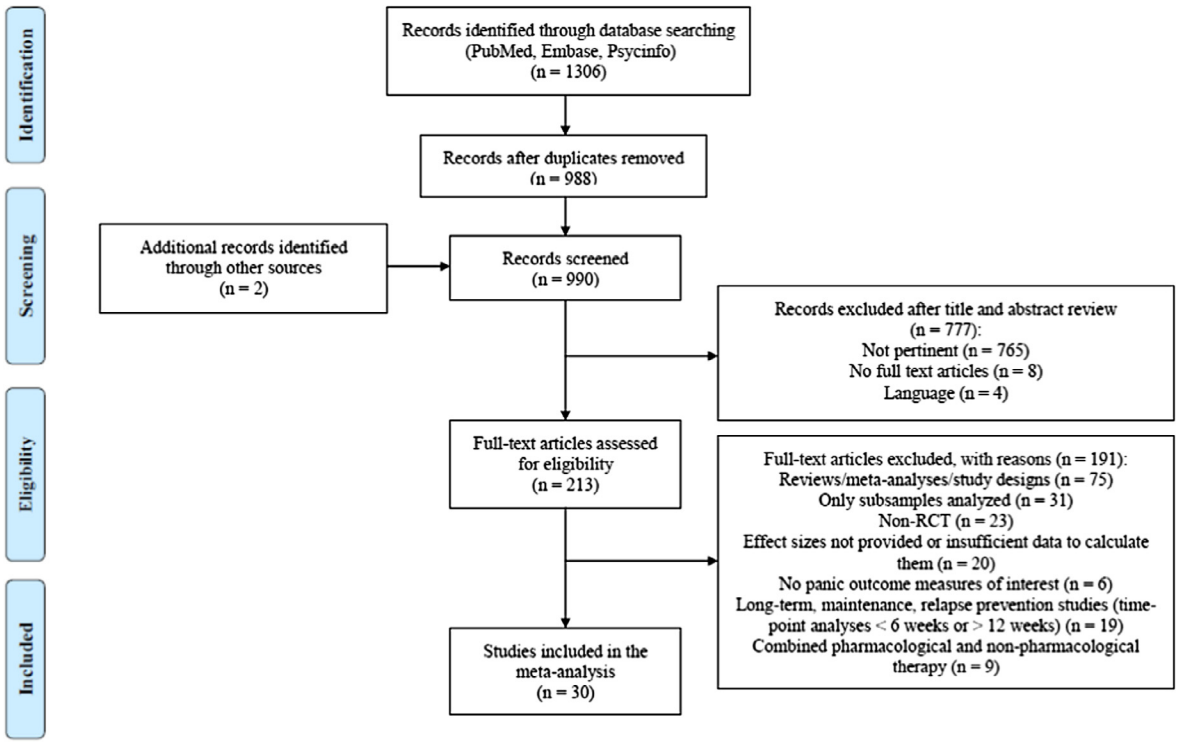

Fig. 1. PRISMA flow diagram of study selection process

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