Journal of Psychiatric Research 94 (2017) 96–106

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Early improvement as a resilience signal predicting later remission to antidepressant treatment in patients with Major Depressive Disorder: Systematic review and meta-analysis

Stefanie Wagner [a, *], Alice Engel [a], Jan Engelmann [a], David Herzog [a], Nadine Dreimüller [a], Marianne B. Müller [a], André Tadić [a, b], Klaus Lieb [a, **]

[a] Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes-Gutenberg-University, Mainz, Germany
[b] Agaplesion Elisabethenstift, Department of Psychiatry, Psychosomatics and Psychotherapy, Darmstadt, Germany

ARTICLE INFO

Article history:
Received 2 January 2017
Received in revised form
2 July 2017
Accepted 2 July 2017

Keywords:
Major Depressive Disorder
Early improvement
Antidepressants
Remission
Meta-analysis

ABSTRACT

Early improvement of depressive symptoms during the first two weeks of antidepressant treatment has been discussed to be a resilience signal predicting a later positive treatment outcome in patients with Major Depressive Disorder (MDD). However, the predictive value of early improvement varies between studies, and the use of different antidepressants may explain heterogeneous results. The objective of this review was to assess the predictive value of early improvement on later response and remission and to identify antidepressants with the highest chance of early improvement. We included 17 randomized controlled trials investigating early improvement in 14,779 adult patients with MDD comparing monotherapy with an antidepressant against placebo or another antidepressant drug. 62% (range: 35–85%) of patients treated with an antidepressant and 47% (range: 21–69%) with placebo were early improver, defined as a >20%/25% symptom reduction after two weeks of treatment. Early improvement predicted response and remission after 5–12 weeks of treatment with high sensitivity (85%; 95%-CI: 84.3 to 85.7) and low to moderate specificity (54%; 95%-CI: 53.1 to 54.9). Early improver had a 8.37 fold (6.97–10.05) higher likelihood to become responder and a 6.38 fold (5.07–8.02) higher likelihood to be remitter at endpoint than non-improver. The highest early improver rates were achieved in patients treated with mirtazapine or a tricyclic antidepressant. This finding of a high predictive value of early improvement on treatment outcome may be important for treatment decisions in the early course of antidepressant treatment. Further studies should test the efficacy of such early treatment decisions.

Contents

1. Introduction 97
   1.1. Aims of the study 97
2. Material and methods 97
   2.1. Study selection 97
   2.2. Data sources and search strategy 97
   2.3. Data extraction 97
   2.4. Outcome parameters 98
   2.5. Statistics 98
3. Results 98
   3.1. Frequency of early improvement 98

* Corresponding author. Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes-Gutenberg-University Mainz, Untere Zahlbacher Straße 8, 55131 Mainz, Germany..
** Corresponding author. Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes-Gutenberg-University Mainz, Untere Zahlbacher Straße 8, 55131 Mainz, Germany.
E-mail addresses: stefanie.wagner@unimedizin-mainz.de (S. Wagner), klaus.lieb@unimedizin-mainz.de (K. Lieb).

http://dx.doi.org/10.1016/j.jpsychires.2017.07.003
0022-3956/

3.2. Predictive value of early improvement on response at endpoint 98
3.3. Predictive value of early improvement on remission at endpoint 99
3.4. Meta-analysis of the predictive value of early improvement at day 14 on response and remission at the end of treatment 99
4. Discussion 101
4.1. Meta-analysis of the predictive value of early improvement at week 2 on response and remission at the end of treatment 101
4.2. Differences between antidepressants 103
4.3. Limitations 104
4.4. Implications for treatment with antidepressants and research 104
Role of funding source 104
Authorship and contributorship 104
Declaration of competing interests 104
Acknowledgements 105
Supplementary data 105
References 105

1. Introduction

Major depressive disorder (MDD) is a highly prevalent and severe psychiatric disorder accompanied by increased suicide rates and is the second among all diseases for disability adjusted loss in life years (DALYs) (Ferrari et al., 2013; Wittchen et al., 2011; Mathers and Loncar, 2006; Kessler et al., 2003).

The use of antidepressant drugs (ADs) for the treatment of MDD is well established. However, a large proportion of individuals with depression do not respond to the first antidepressant requiring a switch to another antidepressant or augmentation with a second drug (Iniesta et al., 2016; Uher et al., 2012; Fournier et al., 2010). An important question raised in this context is, how long treatment with a particular antidepressant should be continued before the attempt is considered as ineffective and the treatment strategy has to be modified. Taking into account that continuing with an ineffective treatment is associated with prolonged suffering, disability and increased risk for suicide for the patient, it should be discontinued (Iniesta et al., 2016; Uher et al., 2011). On the other hand, an early optimization or change of a treatment bearing the potential to become fully effective later on leads to a subsequent narrowing of the therapeutic repertoire and may expose patients to less well-tolerated antidepressants, second-line treatment choices or unnecessary drug combinations (Nakajima et al., 2011).

Most treatment guidelines for MDD recommend the administration of antidepressants for 3–8 weeks based on the idea of a delayed onset of antidepressants action (DGPPN et al., 2015; Bauer et al., 2015; APA, 2011). Contrary to such conventional beliefs, several previous studies have indicated that antidepressants start to exert their efficacy as early as during the first two weeks of treatment (Nierenberg et al., 2000; Katz et al., 2004; Papakostas et al., 2006; Posternak and Zimmerman, 2005; Taylor et al., 2006; Stassen et al., 2007; Leuchter et al., 2009). This early symptom reduction has been proposed to be a good predictor for remission of depressive symptomatology at the end of treatment, while lack of early improvement predicts an unfavourable treatment outcome (Nierenberg et al., 2000; Katz et al., 2004; Papakostas et al., 2006; Posternak and Zimmerman, 2005; Stassen et al., 2007). Thus, an effective antidepressant treatment leading to an early improvement appears to trigger a resilience mechanism necessary for a later recovery of the symptomatology (Stassen et al., 2007).

1.1. Aims of the study

The objective of this systematic review and meta-analysis was to assess the predictive power of early improvement on later response and remission of MDD and to determine possible differences in predictive power (sensitivity & specificity) for later response and remission between antidepressants.

2. Material and methods

2.1. Study selection

We included randomized, double-blind, placebo-controlled studies in adult patients with acute MDD according to DSM-IV, DSM-III-R or DSM-III (APA, 2004). Studies had to compare a monotherapy with an antidepressant drug against placebo or another antidepressant; and had to employ a valid rating scale for the measurement of severity of depressive symptomatology (e.g., the Hamilton Depression Rating Scale [HAMD] (Hamilton, 1960), the Montgomery-Åsberg Depression Rating Scale [MADRS] (Montgomery and Åsberg, 1979)). They had to include information on early improvement defined as a $\geq$20, $\geq$25, or $\geq$30% reduction of depressive symptoms in the first two weeks (day 7 or 14) of treatment, on treatment duration and protocol. To achieve a high standard of reporting, we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the revised Quality Of Reporting Of Meta-analyses (QUOROM) statement (Moher et al., 2009).

2.2. Data sources and search strategy

Peer-reviewed papers published in English were identified through Medline, Embase, Web of science, Cumulative Index to Nursing and Allied Health (CINAHL), PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrial.gov, and the trial databases of the US Food and Drug Administration, the UK Medicines and Healthcare products Regulatory Agency, the European Medicines Agency, and the Australian Therapeutic Goods Administration. The search terms were: (Early Improvement) OR (Early Response) AND Major Depressive Disorder OR Depression AND (antidepressant treatment) OR antidepressants OR (treatment outcome) OR remission. The last update of the search was conducted on July 07th, 2016 without any restriction of publication date. We subsequently checked the reference sections of the publications found in order to identify additional studies that may have been missed. Direct e-mail communication with some researchers also provided additional data sets.

2.3. Data extraction

The following data were extracted from the selected studies by two independent reviewers (SW, AE): criteria used to establish the