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Combining psychopharmacotherapy and psychotherapy is not associated with better treatment outcome in major depressive disorder - evidence from the European Group for the Study of Resistant Depression

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ABSTRACT

Despite plenty of effective antidepressant (AD) treatments, the outcome of major depressive disorder (MDD) is often unsatisfactory, probably due to improvable exploitation of available therapies. This European, cross-sectional, naturalistic multicenter study investigated the frequency of additional psychotherapy in terms of a manual-driven psychotherapy (MDP) in 1410 adult in- and outpatients with MDD, who were primarily treated with AD psychopharmacotherapy. Socio-demographic and clinical patterns were compared between patients receiving both treatments and those lacking concomitant MDP. In a total of 1279 MDD patients (90.7%) with known status of additional MDP, those undergoing a psychopharmacotherapy-MDP combination (31.2%) were younger, higher educated, more often employed and less severely ill with lower odds for suicidality as compared to patients receiving exclusively psychopharmacotherapy (68.8%). They experienced an earlier mean age of MDD onset, melancholic features, comorbid asthma and migraine and received lower daily doses of their first-line ADs. While agomelatine was more often established in these patients, MDD patients without MDP received selective serotonin reuptake inhibitors more frequently. These two patient groups did not differ in terms of response, non-response and treatment resistant depression (TRD). Accordingly, the employment of additional MDP could not be related to better treatment outcomes in MDD. The fact that MDP was applied in a minority of patients with rather beneficial socio-demographic and clinical characteristics might reflect inferior accessibility of these psychotherapeutic techniques for socially and economically disadvantaged populations.

1. Introduction

The enormous global societal and economic burden of major depressive disorder (MDD) (Vos, Allen C et al., 2016) is underlined by the fact that the incidence of MDD has doubled within the last three decades (Liu et al., 2020) leading to 322 million individuals suffering from this disorder in 2015 (WHO 2007). Even though a plethora of effective evidence-based antidepressant (AD) treatment options is available for MDD, the response- and remission rates remain often unsatisfactory (Bauer et al., 2017; Dold and Kasper 2017). Hence, further refinements as well as off-label treatments are frequently applied in order to achieve adequate improvement of depressive symptoms (Dold et al., 2016; Dold, Bartova et al. 2017, 2018, 2018; Dold et al., 2018; Pjrek et al., 2020). The most obvious approach to counteract outcome

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deficiencies might be a systematic and individualized exploitation of available treatment options, ideally in the course of recommended treatment algorithms (Bartova et al., 2019; Kraus et al., 2019).

Meta-analyses report that psychotherapy (PT) that is performed in the course of the so-called manual-driven psychotherapy (MDP) that is, importantly, characterized by the predetermined duration of the individual PT sessions and the PT-type *per se*, as well as its regularity and the given contentual and setting rationales based on a defined school of thought (Mansfield and Addis 2001), appears to be efficacious in MDD with at least moderate effects (Barth et al., 2013). Further evidence suggests that effect sizes of the various PT-types conducted in terms of MDP, whereby the cognitive behavioral therapy (CBT) currently represents the best and the most investigated school of thought, are in the range of AD psychopharmacotherapy (Cuijpers et al., 2014). However, the reported selection- and further methodological bias associated with the heterogeneous manuals of the respective PT-types ranging from the rather rigorous CBT-techniques to less strictly predefined psychoanalytical approaches question this assumption (Munder and Barth 2018). It is noticeable in this context that current clinical practice guidelines (CPGs) derived from different continents and societies lack consistency with respect to recommendations of the multifaceted treatment options available for MDD, especially in terms of MDP (Bayes and Parker 2018). While there is considerable evidence about a large number of patients treated with AD psychopharmacotherapy and lacking concomitant MDP in the United States (US) (Marcus and Olfson 2010; Olfson and Marcus 2010), comparable investigations of European patients are scarce. Hence, we firstly sought to determine the proportion of MDD patients receiving additional MDP to their ongoing psychopharmacotherapy and secondly, we attempted to identify the related socio-demographic, clinical and psychopharmacotherapeutic characteristics. Finally, we aimed to elucidate associations between the employment of additional MDP and treatment outcome in a large naturalistic sample of MDD patients across different European countries.

2. Materials and methods

2.1. Design of the study

This multicenter, cross-sectional, observational, non-interventional study with a retrospective assessment of treatment response represents a part of the "European Group for the Study of Resistant Depression (GSRD)" (Bartova et al., 2019). The present secondary analyses are based on a project "Clinical and biological correlates of resistant depression and related phenotypes" performed between 2011 and 2016 across ten sites in Austria, Italy (two sites), Belgium, Germany, Greece, France (two sites), Israel, and Switzerland (Dold et al., 2016; Bartova et al., 2019). The study-design and procedures, that were approved by the local ethics committees, have been thoroughly introduced in our previous reports and a recent overview (Dold et al., 2016; Bartova et al., 2019) and are therefore described in a cut-down version. All eligible patients signed the informed consent before study participation.

2.2. Patients

Adult in- and outpatients of both sexes were recruited in university as well as non-academic clinical routine settings in the abovementioned eight European countries. The inclusion criteria comprised the presence of a current major depressive episode (MDE) in the course of MDD according to the DSM-IV-TR (Wittchen et al., 1997) as primary psychiatric diagnosis. Furthermore, an ongoing and adequate psychopharmacotherapy encompassing at least one AD drug administered minimally for four weeks in sufficient daily doses during the current MDE was required (Dold et al., 2016; Bartova et al., 2019). The exclusion criteria comprised any primary psychiatric diagnosis other than MDD and comorbid-substance use disorder present in the previous six months and/or severe personality disorder. According to the naturalistic character of the present investigation the co-occurrence of other psychiatric and somatic comorbidities was allowed. Similarly, additional features occurring during the current MDE as the presence of psychotic and/or melancholic features as well as suicidality for instance did not count as exclusion criterion.

2.3. Clinical assessment

To evaluate socio-demographic, clinical, and treatment characteristics, exclusively experienced and specifically trained psychiatrists performed a thorough clinical examination. Hereby, MDD patients' medical records and the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) were considered. Accordingly, the primary psychiatric diagnosis, psychiatric and somatic comorbidities, as well as specific features during the current MDE were established. In the course of a rigorous assessment of the administered treatment strategies, PT was defined by the provision of CBT, psychoanalytic, systemic or not otherwise specified therapies (e. g. meaning-centered psychotherapy) that were employed in addition to the ongoing psychopharmacotherapy during the current MDE and *per definitionem* followed a rationale or manual of the respective school of thought defined by a certain regularity and a predefined duration of the individual PT-sessions, frames for the duration of the PT-type *per se* as well as the conceptual adherence to various therapeutic rationales/principles (e. g. focus on cognitive distortions and emotional regulation via reconceptualization, transference and countertransference or other concepts). Individual PT-interventions lacking these attributes were not considered.

To assess the severity of depressive symptoms at study entry reflecting a time period after at least four weeks of an adequate AD psychopharmacotherapy, the 21-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960), and the Montgomery and Åsberg Depression Rating Scale (MADRS; current MADRS, cMADRS) (Montgomery and Asberg 1979) were employed. Concurrently, the evaluation of the so-called retrospective MADRS (rMADRS) scores, which were calculated based on the MDD patients' assertions and clinical information from their medical records, was mandatory to estimate the severity of depressive symptoms at the onset of the current MDE. Accordingly, the rMADRS scores representing the full-blown extent of depressive symptoms at the beginning of the current MDE, respectively when AD treatment was initiated, refer to a time period that was at least four weeks prior to study entry. Importantly, the ratings were performed by experienced psychiatrists who underwent specific trainings to guarantee a high level of inter-rater reliability. In line with our previously introduced staging model for treatment outcome, the MADRS total score change (rMADRS – cMADRS) was measured after at least one adequate AD trial that was employed $\geq$ four weeks at sufficient daily dosing (Bartova et al., 2019). In detail, response was defined by a MADRS total score of <22 and a $\geq$50% MADRS total score reduction after an adequate AD trial. Non-response was characterized by a MADRS total score of ≥ 22 and a $<$50% MADRS total score reduction after one adequate AD trial. Treatment resistant depression (TRD) was defined as a non-response to $\geq$ two consecutive adequate AD trials (Bartova et al., 2019). In accordance with our previous evidence, suicidality was evaluated according to the HAM-D item 3 (suicidality) ratings (Dold et al., 2018). Hereby, low degree of the current suicidal risk was characterized by the item-score 1, while moderate to high degree of the current suicidal risk was defined by the item-scores 2–4.

2.4. Statistical analyses

MDD patients were subdivided into two groups according to whether they received additional MDP or not. The related socio-demographic, clinical, and psychopharmacotherapeutic patterns are displayed with descriptive statistics (means, standard deviation (SD), and/or percentages; Supplementary Table). Differences between the groups were, respectively, analyzed using analyses of variance (ANOVAs) for

continuous variables and chi-squared tests for categorical variables (Supplementary Table). The Bonferroni-Holm correction for multiple comparisons was employed and, in case of statistical significance (set at a $p \leq .05$), *post-hoc* analyses of covariance (ANCOVAs, for continuous variables) and logistic regression (for categorical variables) including age, sex, and research center as covariates were performed (Supplementary Table). Version 27 of IBM SPSS Statistics was applied for all analyses.

3. Results

3.1. Sample

In total, 1279 (90.7%) of all 1410 MDD patients (Bartova et al., 2019) stated whether they received additional MDP or not and were, hence, included in the present analyses. The socio-demographic, clinical and psychopharmacotherapeutic patterns of the sample of 1279 MDD patients as well as of the two subgroups according to the provision of MDP (n = 399, 31.2%) versus no additional MDP (n = 880, 68.8%) are displayed in the Supplementary Table. While 292 MDD patients received cognitive behavioral therapy (CBT), 107 patients were treated with other types of MDP. The proportion of MDD patients lacking- and receiving concomitant MDP itemized according to the different PT-types is depicted in Fig. 1.

Summarizing the socio-demographic and clinical profile of the final sample comprising 1279 MDD patients (Supplementary Table), 66.6% of them were females, 96.3% were Caucasians, 51% lived in a partnership, 90.8% suffered from a recurrent MDD, 11% experienced psychotic features, 59.3% melancholic features, 45.1% suicidality, and 33.9% received inpatient treatment during their current MDE. 19.9% of our MDD patients exhibited comorbid anxiety disorders and 1.2% comorbid posttraumatic stress disorders (PTSD), while 45.7% suffered from somatic comorbidities. 24.2% of the MDD patients could be categorized as treatment responders, 34.3% as non-responders and 41.4% developed TRD. 58.7% of the patients were treated with polypharmacy, whereby the mean number of concurrently administered psychopharmacotherapeutics amounted to 2.1 ± 1.2 agents. With respect to the first-line AD treatment, selective serotonin reuptake inhibitors (SSRIs) were administered in 52.8%, serotonin-norepinephrine reuptake inhibitors (SNRIs) in 22.7%, noradrenergic and specific serotonergic ADs (NaSSAs) in 8.9%, tricyclic ADs (TCAs) in 5.3%, agomelatine in 5.1%, noradrenaline-dopamine reuptake inhibitors (NDRIs) in 2.2%, serotonin antagonist and

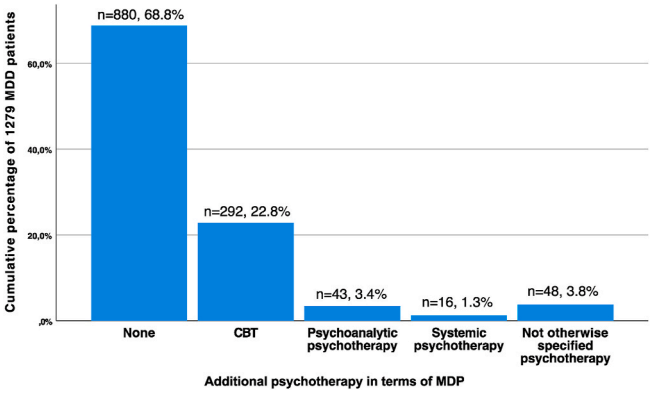

Fig. 1. The Proportion of MDD Patients Lacking and Receiving Psychotherapy in Addition to their Ongoing Psychopharmacotherapy.
Fig. 1 displays the number and the cumulative percentage of MDD patients who were lacking and receiving psychotherapy in terms of MDP (itemized according to its type) that was employed in addition to their ongoing psychopharmacotherapy during the current MDE. Abbreviations (alphabetical order): CBT = cognitive behavioral therapy; MDD = major depressive disorder; MDE = major depressive episode; MDP = manual-driven psychotherapy; n = number.

reuptake inhibitors (SARIs) in 1.8%, vortioxetine in 0.5%, monoamine oxidase inhibitors (MAO-Is) in 0.4%, noradrenaline reuptake inhibitors (NARIs) in 0.2%, and tianeptine in 0.2% of the cases. Regarding add-on psychopharmacotherapies, 28.4% of our MDD patients received a combination treatment with at least one additional AD, whereas 24.9% were additionally treated with antipsychotics, 10.9% with mood stabilizers, and 6.6% with pregabalin. Furthermore, benzodiazepines were co-administered in 31% and the so-called low-potency antipsychotics including all antipsychotic agents with potent sedating properties such as prothipendyl, levomepromazine, as well as low-dose quetiapine <100 mg/day (Dold et al., 2016; Bartova et al., 2019) in 6.2% of the patients.

3.2. Socio-demographic, clinical and treatment characteristics of MDD patients with- and without additional psychotherapy

The below-mentioned differences in terms of socio-demographic, clinical and psychopharmacotherapeutic patterns were detected between MDD patients receiving psychopharmacotherapy-MDP combination versus those treated with psychopharmacotherapy without additional MDP (Supplementary Table). Contrasts withstanding the Bonferroni-Holm correction for multiple comparisons in our initial analyses also remained significant, when age, sex and research center were considered as covariates in our *post-hoc* analyses including ANCOVAs and logistic regression analyses that are displayed in the Supplementary Table in detail.

3.2.1. Socio-demographic patterns

MDD patients undergoing concomitant MDP were younger (46.8 years ±12.9 vs. 51.7 years ±14.4, $p < .001$), higher educated (64.2% vs. 48.7%, $p < .001$) and more often employed (57.5% vs. 43.4%, $p < .001$) compared to MDD patients lacking this treatment option.

3.2.2. Clinical patterns

With respect to the age of MDD onset, patients receiving MDP experienced their first MDE earlier than those without this therapeutic strategy (31.0 ± 14.2 vs. 40.7 ± 15.1, $p < .001$). While melancholic features occurred more often in patients with MDP (76.2% vs. 51.7%, $p < .001$), psychotic features tended to be present in MDD patients receiving exclusively psychopharmacotherapy at an increased proportion (12.2% vs. 8.5%, $p_{uncorrected} = .054$). MDD patients treated with MDP exhibited lower odds for a higher degree of the current suicidal risk (47.9% vs. 62.1%, $p = .001$). Comorbid migraine (20.6% vs. 6.8%, $p < .001$) and asthma (6% vs. 2.3%, $p < .001$) were more often observed in this patient group. Furthermore, lower mean severity of depressive symptoms as measured with the HAM-D (18.8 ± 8.5 vs. 20.6 ± 9.1, $p < .001$) and the cMADRS (23.2 ± 10.3 vs. 25.4 ± 11.5, $p < .001$) at study entry was detected in MDD patients treated with psychopharmacotherapy-MDP combination. In addition, the rMADRS at the onset of the current MDE exhibited a trend in favor of lower scores in MDD patients receiving MDP (33.4 ± 7.5 vs. 34.4 ± 7.7, $p_{uncorrected} = .02$) who also showed a trend towards higher mean reductions of the MADRS total scores during the current MDE (−10.2 ± 10.9 vs. −8.9 ± 10.6, $p_{uncorrected} = .053$). With respect to treatment outcome differentiating between response, non-response and TRD, we did not identify any differences between MDD patients receiving a combination of both treatments and those offered exclusively psychopharmacotherapy ($p = .369$; Table 1; Fig. 2).

3.2.3. Psychopharmacotherapeutic patterns

With respect to the first-line AD treatment, SSRIs were more frequently employed in MDD patients lacking MDP (55.9% vs. 45.9%, $p < .001$), while patients undergoing both treatment options more often received a first-line AD treatment with agomelatine (11.8% vs. 2%, $p < .001$) and, trendwise, vortioxetine (1.3% vs. 0.1%, $p_{uncorrected} = .006$). Generally, mean daily doses of the administered first-line ADs calculated

Table 1
Treatment Outcome of MDD Patients Lacking and Receiving Psychotherapy in Addition to their Ongoing Psychopharmacotherapy.

Treatment Outcome	MDD patients with known status of additional MDP (n = 1279)	MDD patients receiving MDP (n = 399)	MDD patients lacking MDP (n = 880)	x^2	p-value
Response	310 (24.2)	103 (25.8)	207 (23.5)	2.0	.369
Non-response	439 (34.3)	142 (35.6)	297 (33.8)		
TRD	530 (41.4)	154 (38.6)	376 (42.7)		

Table 1 displays the number and the percentages of 1279 MDD patients achieving treatment response, developing non-response, or fulfilling the criteria for TRD (Bartova et al., 2019) who are further itemized according to whether or not they received psychotherapy in terms of MDP that was employed in addition to their ongoing psychopharmacotherapy during the current MDE. Abbreviations (alphabetical order): MDD = major depressive disorder; MDE = major depressive episode; MDP = manual-driven psychotherapy; n = number; TRD = treatment resistant depression.
Bartova, L., M. Dold, A. Kautzky, C. Fabbri, M. Spies, A. Serretti, D. Souery, J. Mendlewicz, J. Zohar, S. Montgomery, A. Schosser and S. Kasper (2019). "Results of the European Group for the Study of Resistant Depression (GSRD) - basis for further research and clinical practice." World J Biol Psychiatry **20**(6): 427–448.

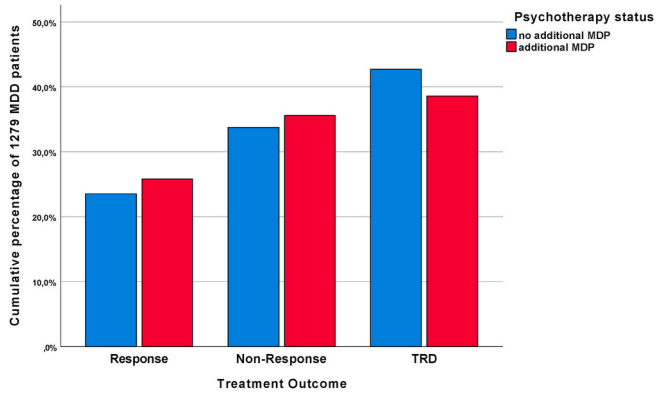

Fig. 2. Treatment Outcome of MDD Patients Lacking and Receiving Psychotherapy in Addition to their Ongoing Psychopharmacotherapy.
Fig. 2 displays the cumulative percentages of MDD patients achieving treatment response, developing non-response, or fulfilling the criteria for TRD (Bartova et al., 2019) who are itemized according to whether or not they received psychotherapy in terms of MDP that was employed in addition to their ongoing psychopharmacotherapy during the current MDE. Abbreviations (alphabetical order): MDD = major depressive disorder; MDE = major depressive episode; MDP = manual-driven psychotherapy; TRD = treatment resistant depression.
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according to fluoxetine dose equivalents (Hayasaka et al., 2015) were higher in MDD patients without additional MDP (41.7 ± 19.0 vs. 36.3 ± 24.4, $p < .001$).

4. Discussion

This large, real-world European cross-sectional study with a retrospective evaluation of treatment response revealed that about one out of three MDD patients was treated by a combination of psychopharmacotherapy and PT in terms of MDP. Precisely, CBT was most commonly applied in around three-quarters of the cases. Taken together, MDD patients receiving additional MDP were younger, higher educated, more often employed and experienced an earlier mean age of MDD onset as compared to MDD patients offered exclusively psychopharmacotherapy. While melancholic features, comorbid asthma and migraine occurred more frequently in patients undergoing both treatments, overall depression severity and suicidality were less pronounced. Furthermore, first-line AD treatment with SSRIs was less commonly established, whereas agomelatine was more often prescribed together with MDP. Generally, daily doses of the administered first-line ADs were lower than in MDD patients lacking concomitant MDP. The combination of psychopharmacotherapy and MDP was not associated with a favorable treatment outcome.

Previous US evidence on therapeutic patterns in MDD indicated that a psychopharmacotherapy-MDP combination is provided in 20% of all depressed patients with a decreasing trend throughout the last two decades (Marcus and Olfson 2010; Olfson et al., 2016). The proportion of MDP that was employed in addition to the ongoing psychopharmacotherapy was even lower than in our investigation and a clear parallel could be drawn regarding socio-demographic aspects. Older, less educated and unemployed patients exhibited significantly lower odds for additional MDP in both, US and European samples, which might reflect worse access to these psychotherapeutic techniques in MDD patients with potential economic and social disadvantages (Olfson et al., 2016). The latter findings are consistent with further reports underlining an obviously low utilization of MDP in depressed outpatients in Germany reflecting a real care situation that is very much in contrast with recommendations for a broad use of MDP in the national treatment guidelines (Möller 2014). Hereby, further background factors like a different availability and extent of psychiatric and psychotherapeutic care in urban- and rural areas, long waiting times due to an insufficient number of respective experts, potential arbitrary selection processes related to specific disease and/or patient characteristics, as well as differences in terms of acceptance and implementation resulting from varying treatment settings that range from general practitioners' offices to specialized psychiatric and psychotherapeutic institutions, were shown to explain the discrepancy in the utilization of MDP (Möller 2014).

An obvious and pursuing question, particularly in times of striving precision treatments in MDD, is who benefits most from which type of MDP (Furukawa et al., 2018). In fact, only a limited proportion of studies conducted in these regards are considered of high quality with low risk of bias (Trivedi et al., 2011; Jakobsen 2014). What current evidence reveals so far is that MDP shows comparable efficacy for many groups of MDD patients regardless of age, sex, or somatic comorbidities (Cuijpers et al., 2018). A second crucial point is that different forms of MDP appear to be efficacious in MDD. Hereby, CBT in its original as well as further formats, that were adapted according to the individual patients' needs, represents the currently best investigated form of MDP and is, hence, recommended for the treatment of MDD and TRD in most international guidelines (Trivedi et al., 2011; Jakobsen 2014; Jobst et al., 2016; Nakagawa et al., 2017; Bockting et al., 2018; Furukawa et al., 2018; van Bronswijk et al., 2019). A recent review and meta-analysis focusing on augmentation treatments for TRD found modest evidence for MDP that was represented by only three studies investigating CBT, mindfulness-based CBT and long-term psychoanalytic PT (Strawbridge et al., 2019). Although the efficacy of augmentation with MDP and psychopharmacotherapy was shown to be comparable in this meta-analysis, the authors highlighted the unequal amount of studies investigating either MDP or psychopharmacotherapeutics and, hence, emphasized the requirement for a more intensive investigation of psychological treatments (Husain et al., 2019).

Based on recent findings, CBT was reported to be beneficial in older populations, as well as in university students and in case of comorbid addiction disorders (Cuijpers et al., 2016). In our sample, MDD patients treated with psychopharmacotherapy and additional MDP, that was CBT in the most cases, were younger and, concurrently, more often suffered from migraine and asthma as comorbid conditions than patients lacking

this treatment option. In analogy, previous evidence on MDD and comorbid chronic pulmonary disease proved effectivity of MDPs in reducing both depressive and respiratory symptoms, while focusing on overcoming barriers of treatment and promoting adherence to medication and healthier lifestyle (Alexopoulos et al., 2013). In depressed migraineurs, CBT led to reductions of headache and depressive symptoms simultaneously (Martin et al., 2015), supporting the obvious benefits of MDP, and CBT in particular, for MDD with comorbid somatic diseases. An auspicious finding in this context is that different formats of CBT, including group and remote interventions, that are more cost-effective and better accessible than individual therapies, seem to exhibit similar effects (Kamenov et al., 2017), and could therefore be preferably applied to a broader patient population including individuals who are potentially disadvantaged in terms of socio-demographic, economic and/or disease factors.

With respect to severity of depressive symptoms, the present study revealed overall lower scores regarding the HAM-D and the MADRS as well as a lower degree of suicidal risk in MDD patients treated with a psychopharmacotherapy-MDP combination as compared to those receiving exclusively psychopharmacotherapy. The latter results might support previous evidence considering psychopharmacotherapy-MDP combination beneficial in terms of preventing suicides (Zalsman et al., 2016) with the best available proof of concept existing for CBT, whereby the treatment success might be attributable to a direct discussion of suicidal ideations and behaviors (Calati et al., 2018). On the other hand, the less severe disease manifestation in our MDD patients receiving both treatments might further underline the abovementioned arbitrary selection bias in terms of referring preferably patients with milder symptom profiles lacking suicidal risk to MDP which is also a common position in international guidelines for the management of MDD (Pilling et al., 2009; Möller 2014; Bauer et al., 2017). This reflects the unequal distribution of available treatment strategies in the broad clinical routine.

In terms of specific symptom manifestations, our MDD patients suffering from melancholic features more frequently underwent a psychopharmacotherapy-MDP combination, while those with psychotic symptoms tended to be less commonly treated with additional MDP. In this context it is noteworthy that generally symptoms inherent to melancholia, anhedonia, psychomotor disturbances, and/or psychotic phenomena were shown to respond well to biological treatments including psychopharmacotherapy, most likely due to repeatedly identified neurobiological correlates as dysregulation of the hypothalamic-pituitary-adrenal axis for instance (Bauer et al., 2017; Dold and Kasper 2017; Dold et al., 2019; Kraus et al., 2019). Despite the fact that our results point towards a more frequent use of additional MDP in MDD patients suffering from melancholic features, which may appear counter intuitive at first glance, it is worth to mention in this regard that indications from the literature about the efficacy of MDP in MDD with melancholic features lack consistency. While results of randomized-controlled trials (RCTs) comparing CBT and AD psychopharmacotherapy in melancholic depression delivered evidence in favor of psychopharmacotherapy as first-line AD treatment (Parker et al., 2013; Gilfillan et al., 2014), a recent meta-analysis observed little and insignificant differences between the efficacy of either CBT or AD psychopharmacotherapy as the first-choice treatment for melancholic and atypical depression (Cuijpers et al., 2017). Overall, available international evidence provide convincing arguments against MDP as treatment option of first choice in such MDD patient populations who might have difficulties to engage to interventions of psycho-social nature when they suffer from severe depressive symptoms such as melancholic and/or psychotic features (Sharpley and Bitsika 2011; McIntyre et al., 2017). In this context, the so-called sequential combination of psychopharmacotherapy and psychotherapeutic techniques seems to be justified as this approach exhibited advantages over monotherapy in terms of a sustained and more stable treatment response (Karyotaki et al., 2016) as well as the prevention of relapse (Bockting et al., 2018). Hereby, the treatment sequence was suggested to be initiated by psychopharmacotherapy that directly interferes with the neurobiological underpinnings of MDD and, hence, represents the first-line treatment of MDD and its therapeutic basis respectively (Kranz and Kasper 2019). Once the administered psychopharmacotherapy showed effectivity in terms of improvement of depressive symptoms as well as in functionality and quality of life, patients may profit from the employment of additional MDP, especially when they suffer from residual symptoms (Guidi and Fava 2021). Such sequential integration of MDP following response to acute-phase psychopharmacotherapy was shown to reduce the risk of relapse and recurrence and, hence, appears to be particularly indicated in recurrent and chronic depression (Guidi and Fava 2021).

Being aware that cross-sectional evaluations are unsuitable to draw causal conclusions, we would like to highlight that our MDD patients receiving additional MDP did not differ from patients offered exclusively psychopharmacotherapy in terms of treatment outcome. Although MDD patients undergoing psychopharmacotherapy-MDP combination showed a trend towards greater reduction of MADRS total scores during the current MDE, the rates of response, non-response and TRD were comparable regardless of the provision of concomitant MDP. Accordingly, the integration of MDP does not seem to suffice to overcome TRD, a condition that was repeatedly shown to respond to rather biologically-oriented therapies such as psychopharmacotherapeutic augmentation and combination treatments or electroconvulsive therapy for instance (Kraus et al., 2019).

On the other hand, the fact that treatment outcome was not influenced by additional psychotherapeutic approaches in terms of MDP might be associated with the ambiguous and potentially misunderstandable definition of MDP *per se*, which is mostly characterized by sessions at regular intervals that last approximately 50 min in the most cases regardless of the applied school of thought predefining the setting, frequency and the procedural alignment of the applied PT-type. The fact that MDP including rather rigorous CBT-techniques as well as less strictly predefined psychoanalytical approaches can be provided by diverse experts with heterogeneous educational levels and specifications comprising psychiatrists, psychotherapists, clinical psychologists and further specialists may result in a varying quality with potential effects on treatment outcome. In this context, we would like to point out that a comprehensive psychotherapeutic education is mandatory for completing psychiatric specialization as medical discipline in some, but not all European countries including Austria, Germany and Switzerland. Hereby, the official certification and professional title obtained is called “specialist for psychiatry and psychotherapeutic medicine” in Austria and “specialist for psychiatry and psychotherapy” in Germany and Switzerland. The specific title “specialist for psychiatry and psychotherapeutic medicine” in Austria has been thoughtfully considered and explicitly formulated over years and is thought to appropriately describe the psychiatrists’ daily routine including a simultaneous integration of neurobiological as well as psychotherapeutic approaches. In detail, psychiatrists are physicians undergoing extensive training in all medical fields to obtain their medical degree who subsequently receive a comprehensive clinical training in both, psychopharmacotherapeutic and non-pharmacological treatments of the full spectrum of psychiatric disorders to complete their specialization in psychiatry. Given this educational process lasting about ten years in the countries mentioned above psychiatrists experience a broad scope of understanding of the nature and course of psychiatric diseases as well as their multifaceted treatment options. Hence, they deem it a privilege to be able to provide psychotherapeutic interventions in the course of the individual treatment concepts, in terms of the sometimes depreciatingly called “supportive PT” that, however, represents an essential aspect of each clinical interaction even though the criteria of MDP may not be completely covered. Exemplarily, a short individual psychoeducational or motivational support towards positive mental health and general well-being, that is feasible during the regular rounds at psychiatric hospitals and/or consultations at outpatient units, might represent a very effective

psychotherapeutic intervention, which may significantly contribute to the overall beneficial effects together with ongoing psychopharmacotherapy and/or other modality of the broad armamentarium of available treatment strategies. In summary, the comparable treatment outcomes between our MDD patients who were receiving- and lacking additional MDP might be attributable to the aforementioned supportive psychotherapeutic interventions that were successfully implemented in some of our patients by psychiatrists in charge and that were, however, not officially assessed, since the official definition for MDP was not met.

Looking at the administered psychopharmacotherapy, SSRIs were less commonly prescribed as first-line AD treatment in MDD patients receiving a psychopharmacotherapy-MDP combination. Agomelatine and, trend-wise, vortioxetine in contrast were more frequently administered to that patient group. While SSRIs represent the recommended first-line AD treatment that is commonly very well accessible in the most countries worldwide, agomelatine and vortioxetine constitute modern and effective alternatives in the course of a first-line AD treatment that, however, are far less available and mostly not covered by public health-insurance (HI) systems. Although we did not find any compelling evidence in comparable international samples of MDD patients, we tend to interpret this observation in relation to the rather favorable socio-demographic characteristics identified in our MDD patients undergoing both treatment strategies who might have better access to treatments beyond those covered by the public HI systems. However, the latter considerations represent subject to certain caveats, as the prescription rates of agomelatine and vortioxetine were very small.

The overall lower daily doses of the applied ADs identified in the group of MDD patients receiving both therapies might be explained by a less severe disease profile associated with receiving additional MDP, a lesser focus on psychopharmacotherapy while undergoing MDP, or potential lesser need of dose escalations due to the additional psychotherapeutic interventions. It is noteworthy in this context that dose escalation failed to show superiority over the continuation of standard-dose AD treatment in MDD in the most studies (Dold et al., 2017), and was repeatedly associated with greater odds for unwanted side-effects (Jakubovski et al., 2016) and potential discontinuation symptoms, which might occur during tapering and discontinuation of ADs (Fava et al., 2018).

Strengths of the present study include the naturalistic design constructing a realistic picture of psychiatric care including the provision of MDP in MDD by comprising differently aged adult patients of both sexes who were at different stages of treatment and who suffered from a varying severity of depressive symptoms comprising suicidality, psychotic features and comorbidities, that are considered as exclusion criteria in the majority of available studies. Another major strength is the large sample size derived from different treatment settings including in- and outpatient units in university-as well as non-academic centers across eight European countries.

Concerning limitations, it has to be pointed out that this study was primarily executed to investigate TRD (Bartova et al., 2019), whereby the present secondary analysis of the impact of additional MDP in MDD patients receiving primarily psychopharmacotherapy represents an additional aspect. Hereby, the information about which treatment strategy was commenced or seemed to be pivotal is missing. Further intrinsic limitations linked to the fact that the present study was not originally designed to test this hypothesis represent limited knowledge concerning the reason for initiating MDP as well as its exact duration. Due to the identified socio-demographic and clinical differences between both patient groups a possible selection bias associated with distinct patient- and/or disease factors cannot be fully ruled out. While the majority of our MDD patients was treated with CBT, a comparably small proportion of the remaining patients underwent MDPs according to different schools of thought. Hereby, we did not differentiate between the distinct psychotherapeutic specifications, which we deem justifiable in light of the fact that superiority of a specific PT school could not be demonstrated with certainty (Cuijpers 2016) and due to the small number of MDD patients treated with other MDPs in general. With respect to the administered psychopharmacotherapy, it is worth to mention that our MDD patients received conventional on-label treatments, whereby promising novel antidepressant agents like esketamine (Kraus et al., 2019; Kasper et al., 2020; Sanders Benjamin 2021) have not yet been considered. Most importantly, it should be highlighted that the data analyzed in the present study were derived from a cross-sectional investigation with retrospective evaluation of treatment outcome. This may represent a major limitation when the reported findings are compared with results derived from prospective randomized-controlled longitudinal trials. The concept of retrospective evaluation of treatment response, that is undoubtedly less accurate than prospective approaches, however, might enable a very likely exemplification of the real care situation without any distortion due to the related inclusion bias. Furthermore, it is worth to note in this context that the retrospective assessment in our study was performed according to rigorously predetermined conditions exclusively by experienced psychiatrists who underwent specific trainings to guarantee a high level of inter-rater reliability that was, however, not specifically investigated with respect to the rMADRS. Hereby, the rMADRS reflecting the full-blown extent of depressive symptoms at the beginning of their current MDE, respectively when their AD treatment was initiated, referred to a time period that was at least four weeks prior to study entry. Being aware of the relevant methodological limitation of retrospective ratings, available international evidence revealing that MDD patients are able to adequately report retrospective symptoms of their MDEs even two years thereafter (Dunlop et al., 2019) supports that the applied approach is not too far-fetched. The latter assumption might be further underlined by the fact that our retrospective evaluations reflect a markedly shorter time period of four and more weeks thereafter as compared to a time period of two years thereafter which was previously suggested as adequate for retrospective ratings (Dunlop et al., 2019). Taken together, we consider our approach justifiable.

5. Conclusion

The abovementioned cross-sectional and retrospective analyses revealed that merely about one-third of the present naturalistic sample of MDD patients was treated by a psychopharmacotherapy-MDP combination, which is in contrast to most available treatment recommendations. The fact that receiving additional MDP was associated with beneficial socio-demographic characteristics as younger age, higher educational level and ongoing employment points towards a reluctance of exploiting available treatment options to the fullest and evinces significant barriers especially in socially and economically disadvantaged populations. The association of favorable clinical aspects like a lower extent of depression severity and lower odds for suicidality with the provision of additional MDP in our study might be explained by a selection bias leaving patients with a more severe illness profile fall by the wayside. Finally, it should be highlighted that the employment of additional MDP was not associated with a superior treatment outcome in our population of adult MDD in- and outpatients, which might emphasize the fundamental role of the underlying complex biological interrelationships in MDD and its treatment.

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Statement of Ethics

The present research complies with internationally-accepted

standards for research practice and reporting, and has been performed with approvals of appropriate ethics committees and with appropriate participants' informed consent in compliance with the Helsinki Declaration.

Authorship statement

Dr. Bartova and Dr. Fugger contributed to designing the study, implementation of the research, statistical analyses, and writing the report including the first draft of the manuscript. Dr. Kasper contributed to designing the study, implementation of the research, and writing the report. All authors contributed to implementation of the research and have critically revised and approved the final manuscript.

Declaration of competing interest

Dr. Bartova has received travel grants and consultant/speaker honoraria from AOP Orphan, Medizin Medien Austria, Vertretungsnetz, Schwabe Austria, Janssen and Angelini. Dr. Dold has received travel grants and consultant/speaker honoraria from Janssen-Cilag. Dr. Zohar has received grant/research support from Lundbeck, Servier, and Pfizer; he has served as a consultant or on the advisory boards for Servier, Pfizer, Solvay, and Actelion; and he has served on speakers' bureaus for Lundbeck, GlaxoSmithKline, Jazz, and Solvay. Dr. Mendlewicz is a member of the board of the Lundbeck International Neuroscience Foundation and of the advisory board of Servier. Dr. Souery has received grant/research support from GlaxoSmithKline and Lundbeck; and he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen, and Lundbeck. Dr. Montgomery has served as a consultant or on advisory boards for AstraZeneca, Bionevia, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Grunenthal, Intellect Pharma, Johnson & Johnson, Lilly, Lundbeck, Merck, Merz, M's Science, Neurim, Otsuka, Pierre Fabre, Pfizer, Pharmaneuroboost, Richter, Roche, Sanofi, Sepracor, Servier, Shire, Synosis, Takeda, Theracos, Targacept, Transcept, UBC, Xytis, and Wyeth. Dr. Fabbri has been supported by Fondazione Umberto Veronesi (https://www.fondazioneveronesi.it). Dr. Serretti has served as a consultant or speaker for Abbott, Abbvie, Angelini, AstraZeneca, Clinical Data, Boehringer, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Innovapharma, Italfarmaco, Janssen, Lundbeck, Naurex, Pfizer, Polifarma, Sanofi, and Servier. Within the last three years, Dr. Kasper received grants/research support, consulting fees, and/or honoraria from Angelini, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Mundipharma, Neuraxpharm, Pfizer, Sanofi, Schwabe, Servier, Shire, Sumitomo Dainippon Pharma Co. Ltd., sun Pharma and Takeda. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.06.028.

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