Journal of Affective Disorders 325 (2023) 7–13

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Review article

When to stop medication in unipolar depression: A systematic review and a meta-analysis of randomized controlled trials

Mehmet Kemal Arıkan [a], Reyhan İlhan [a], Oliver Pogarell [b], Barış Metin [c,*]

[a] Kemal Arıkan Psychiatry Clinic, Istanbul, Turkey
[b] Department of Psychiatry, Division of Clinical Neurophysiology, Ludwig-Maximilians-University of Munich, Munich, Germany
[c] Department of Neurology, Medical Faculty, Uskudar University, Istanbul, Turkey

ARTICLE INFO

Keywords:
Major depressive disorder
Relapse
SSRI
SNRI
Atypical antidepressants
Recurrence
Treatment cessation

ABSTRACT

Background: Currently, there is no clear answer to the question of how long antidepressants should be continued or when they can be safely discontinued.
Methods: Pubmed/Medline was systematically searched from inception to Feb 20, 2021. Double-blind, randomized placebo-controlled trials (RCTs) with maintenance phase were selected to examine the relationship between relapse rate and treatment duration. Among 5351 screened records, 37 RCTs meeting inclusion criteria were selected. Odds ratios were calculated from relapse rates for each study and pooled in random-effect models. Possible predictors of effect sizes, i.e., open-label treatment duration, double-blind phase duration, age, medication type, history of recurrence, were analyzed by meta-regression.
Results: The random-effects model showed the superiority of active medication over placebo for relapse during the follow-up phase (OR = 0.37; 95 % CI, 0.32–0.42). The meta-regression did not show a relationship between treatment duration and the effect sizes. Other clinical variables were not related with effect sizes. Subgroup analysis revealed that, for atypical ADs the effect size increased as the treatment duration increased. Further analysis showed that the relapse rate in the placebo group decreased as function of time, which reduced the absolute benefit of continued treatment.
Conclusion: The results may indicate that long term use of antidepressants may not be justified, and this strategy may expose the patients to more adverse effects.

1. Introduction

Major depressive disorder (MDD) is a disabling health problem globally due to significant amount of hospital admissions, medication use, workload loss and death. Compared to pre-pandemic period, the prevalence of depression has more than doubled (OECD, 2021). In addition to high prevalence rates, the short-term and long-term use of antidepressants is rising (Huijbregts et al., 2017; Mars et al., 2017; Meijer et al., 2004).

A significant majority of individuals with depression are considered recurrent depressives as their depression will recur by 60 % after the first episode (American Psychiatric Association, 2013). Currently, the clinical guidelines for the treatment of depression recommend long-term treatment with anti-depressants for patients with recurrent depression (Bauer et al., 2015; Gelenberg et al., 2010; Kennedy et al., 2016; Malhi et al., 2021; National Collaborating Centre for Mental Health, 2010; Psychological Association, 2019; The Management of Major Depressive Disorder Working Group, 2016). On the other hand, the duration of treatment is not certain. Concerning treatment duration, an analysis compared relapse rates of MDD patients based on the duration of AD use, i.e., <4, 4–6, 7–9, and 10–12 months, respectively, and proposed that a minimum of 10–12 months of treatment is necessary. Nevertheless, one-third of these patients relapsed despite relatively long-term treatment (Liu et al., 2021).

The relapse prevention studies, designed to investigate long-term effects of antidepressants over placebo, report prophylactic effects by the difference between relapse rates. However, real-world trials failed to find this effect. Therefore, risk-benefit evaluation is necessary for the long-term use of ADs is crucial (Hengartner, 2020). To demonstrate the overall effect of ADs over placebo on relapse and to find out if ADs were effective as maintenance therapy, a previous meta-analysis was conducted on patients in remission (Kato et al., 2021). They found that

* Corresponding author at: Psychology Department, Üsküdar University, Altunizade Haluk Türksoy Sk. No:14, 34662, Üsküdar, İstanbul, Turkey.
E-mail address: baris.metin@uskudar.edu.tr (B. Metin).

https://doi.org/10.1016/j.jad.2023.01.024
Received 28 July 2022; Received in revised form 26 December 2022; Accepted 4 January 2023
Available online 6 January 2023

relapse was 20 % lower on medication compared to placebo (Kato et al., 2021). Furthermore, treatment duration, double-blind phase duration, and AD type did not influence the relapse rate. On the other hand, older people have similar relapse rates as the adult population, while younger patients are more likely to relapse after discontinuation of ADs. Titrated dose of ADs reduces relapse rates compared to fixed dose. The authors suggest that the first 6 months after treatment cessation is crucial for relapse and SSRIs treatment is much more balanced considering acceptability and tolerability (Kato et al., 2021).

The long-term use of ADs should be evaluated for cost-effectiveness as it leads to several problems. Firstly, the prescription of antidepressants in unnecessary conditions places a significant economic burden on many healthcare services (Davies et al., 2022; Papanicolas et al., 2018; Shrank et al., 2019). Additionally, prolonged use of ADs is limited by the safety issues including drug-drug interactions and side effects related to these medications (Clark et al., 2012), especially for geriatric populations (Mark et al., 2011). Even new generation antidepressants with better safety profiles have considerable side effects that were considered "bothersome" by more than half of the patients (Cascade et al., 2009). Among those, the most notable ones are gastrointestinal problems, dermatologic and vascular reactions, weight gain, genitourinary problems, sexual dysfunction, central nervous system problems (Carvalho et al., 2016). Furthermore, the anti-depressants are associated iatrogenic behavioral toxicity such as suicidality, aggression, switch to mania and post-withdrawal symptoms (Fava et al., 2016).

Considering the lack of certain treatment duration and problems related to the long-term use of ADs we aimed to perform a meta-analysis of factors predicting relapse rates and to find out how long the antidepressants should be followed to minimize the relapse. For this goal, we combined the data from double-blind maintenance studies and performed a regression for the effect of treatment duration on the relapse-recurrence rate.

2. Methods

Pubmed search was conducted with the following keywords: depression AND (antidepressant OR SSRI OR SNRI) AND (relapse OR recurrence OR cessation OR "stop medication" OR "stop treatment). Based on the above search terms we identified 5351 studies. The study eligibility decisions were made after inspection by one of the researchers and the results were double-checked. After the eligibility criteria application, we identified the studies that can be included in the analysis. The PRISMA flow chart for the study selection can be found in Fig. 1.

2.1. Eligibility criteria

The articles were reviewed according to the following inclusion criteria:

1. Randomized double-blind follow-up studies in which patients were randomized to active or placebo arms after an open-label treatment phase
2. The patient group only included patients with major depression
3. The diagnosis was established according to one of the DSM versions

Exclusion criteria were defined as follows:

1. Lack of a placebo control group
2. Comorbidity of a psychotic disorder or presence of bipolar disorder
3. Combined treatment with more than one medication

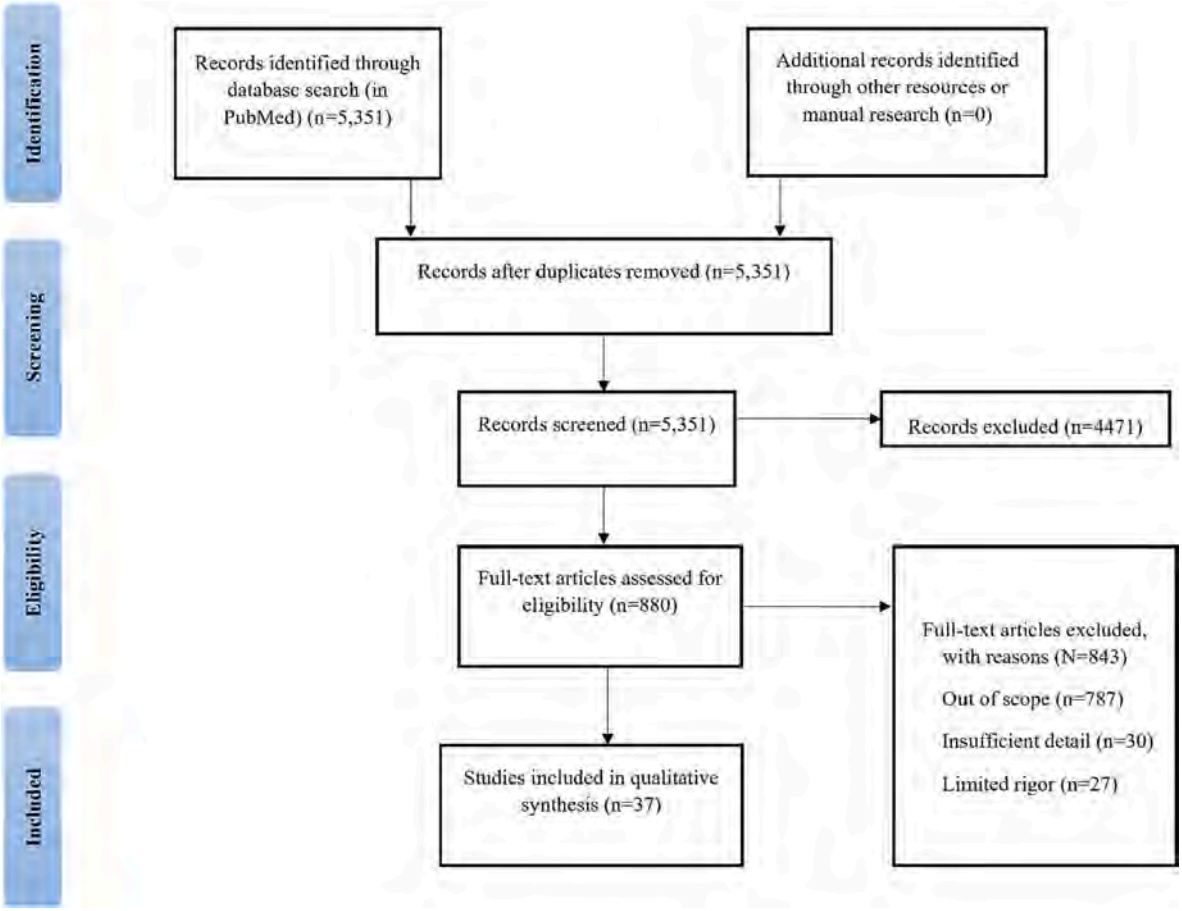

Fig. 1. PRISMA flowchart. The chart indicates the number of included and excluded articles for meta-analysis.

4. Studies combining pharmacotherapy with psychotherapy

2.2. Data extraction

The extracted variables included medication type, open label and double-blind durations, age, presence of treatment resistance, recurrence, or high risk of relapse in the study population. The latter group included studies that recruited individuals with recurrent or chronic depression.

2.3. Statistical analysis

Statistical analysis was conducted on Comprehensive Meta-Analysis Software — CMS (Version 3, Biostat Incorporation).

2.3.1. Primary analysis

Due to presumed heterogeneity, we chose random-effects model for the meta-analysis. First, we calculated the odds ratio for all studies and performed random-effects meta-analysis.

2.3.2. Secondary analysis

Then, we examined the regressions for the association of open-label and double-blind phase durations on effect size.

2.3.3. Subgroup analysis

Finally, we calculated the event rate for active medication and placebo groups separately to better understand the effect of study duration parameters on relapse rate. For convenience, the studies were divided into 3 groups: 1. Selective-Serotonin Reuptake Inhibitor (SSRI) studies, 2. Serotonin Noradrenaline Reuptake Inhibitor (SNRI) studies, and 3. Atypical antidepressant studies (e.g., vortioxetine, agomelatine, reboxetine, nefazodone, bupropion).

3. Results

3.1. Study characteristics

Thirty-seven randomized controlled trials were accepted as eligible. These studies assessed the efficacy of either Selective-Serotonin Reuptake Inhibitors (k = 19, n = 4249), Serotonin Noradrenaline Reuptake Inhibitors (k = 10, n = 3028), or Atypical Antidepressants (k = 8, n = 2443). Atypical antidepressants are defined as medications that can neither be classified as SSRIs nor SNRIs. The treatment outcome was evaluated either by 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960), 17-item Hamilton Depression Rating Scale (HDRS-21), or Montgomery Åsberg Depression Rating Scale (MADRS).

A total of 9720 MDD patients were included the meta-analysis. Of those, 5397 were in active medication arm and 4323 were in placebo arm during double-blind phase. Subjects' mean (SD) age were 49.50 (13.09) and residual symptoms evaluated by HDRS-17 were 5.37 (1.91). In those RCTs, mean (SD) open-label phase duration were 15.70 (8.29) weeks and double-blind phase duration were 42.78 (18.46) weeks.

3.2. Primary analysis

The study characteristics can be found in Table 1. The random-effects model showed the superiority of active medication for relapse during the follow-up phase with a mean effect size of 0.37 (OR = 0.37; 95 % CI,

Table 1
Study characteristics included in the meta-analysis.

Study name	Medication	N (Medication)	N (Placebo)	Duration (open label)	Duration (double-blind)	Age	Resistance/high risk
(Perahia et al., 2009)	Duloxetine	146	142	34	52	47.1	+
(Montgomery et al., 2004)	Venlafaxine	109	116	24	52	43.8	+
(McGrath et al., 2006)	Fluoxetine	131	131	12	52	37.5	
(Gorwood et al., 2007)	Escitalopram	152	153	12	24	73	
(Lustman et al., 2006)	Sertraline	79	73	16	52	50.5	
(Rouillon et al., 2000)	Milnacipran	104	110	24	52	46.1	+
(Rickels et al., 2010)	Desvenlafaxine	189	185	12	24	42.7	
(Shiovitz et al., 2014)	Levomilnacipran	233	112	12	24	42.2	
(Durgam et al., 2019)	Levomilnacipran	165	159	20	24	44.6	+
(Rapaport et al., 2004)	Escitalopram	181	93	8	36	42.9	
(Rosenthal et al., 2013)	Desvenlafaxine	272	276	20	24	46.6	
(Kornstein et al., 2008)	Venlafaxine	55	59	10	52	41	+
(Kornstein et al., 2006)	Escitalopram	73	66	24	52	42	+
(Simon et al., 2004)	Venlafaxine	161	157	8	24	43	
(Lépine et al., 2004)	Sertraline	189	99	32	72	47	+
(Klysner et al., 2002)	Citalopram	60	61	24	48	74	+
(Hochstrasser et al., 2001)	Citalopram	132	132	22	48	43.8	+
(Keller et al., 1998)	Sertraline	92	107	28	76	40.8	+
(Terra and Montgomery, 1998)	Fluvoxamine	110	94	24	48	44.5	
(Robert and Montgomery, 1995)	Citalopram	152	74	8	24	49.5	
(Boulenger et al., 2012)	Vortioxetine	204	192	12	64	44.8	+
(Durgam et al., 2018)	Vilazodone	371	192	20	18	45.2	
(Doogan and Caillard, 1992)	Sertraline	185	110	8	44	51	
(Montgomery and Dunbar, 1993)	Paroxetine	68	67	8	52	45.9	
(Wilson et al., 2003)	Sertraline	56	57	24	100	76.6	
(Weihs et al., 2002)	Bupropion	207	210	8	44	39.4	+
(Goodwin et al., 2009)	Agomelatine	165	174	8	24	43.2	
(Montgomery et al., 1993)	Citalopram	103	44	6	24	44	
(Feiger et al., 1999)	Nefazodone	65	66	16	36	40	
(Fava et al., 2006)	Duloxetine	136	142	12	26	44.68	
1998 (Reimherr et al., 1998)	Fluoxetine	344	95	12	50	40	
(Thase et al., 2001)	Mirtazapine	76	80	8	40	40.1	+
(Schmidt et al., 2000)	Fluoxetine	189	122	13	25	41.7	
(Gilaberte et al., 2001)	Fluoxetine	70	70	32	48	44.4	+
(Dalery et al., 2001)	Tianeptine	111	74	6	66	44.07	+
(Versiani et al., 1999)	Reboxetine	145	111	6	46	43.4	+
(Kamijima et al., 2006)	Sertraline	117	118	8	16	40.8	+

Note: "+" refers to studies who report drug resistance characteristics of patients. The duration is given in weeks.

0.32–0.42) (Fig. 2).

3.3. Secondary analysis

The meta-regression did not show a significant effect of treatment duration on the effect sizes ($p = 0.7$). In addition, there was no relationship between the duration of the randomized double-blind phase ($p = 0.5$) and the effect size magnitude. A follow-up analysis only included studies with high-risk or recurrent patients did not also reveal any significant results on meta-regression. There was finally no relationship between mean age and effect size ($p = 0.7$).

3.4. Subgroup analysis

The subgroup analysis was performed by separating the studies into three groups: 1. SSRI studies, 2. SNRI studies, and 3. Studies with other (atypical) antidepressants (bupropion, nefazodone, vilazodone, reboxetine, vortioxetine, tianeptine, mirtazapine). The meta-regression with only groups 1 or 2 did not reveal any significant effects. However, there was a positive relationship between effect sizes and open-label treatment duration for the studies in the 3rd group (z = 2.18, slope = 0.07, CI = 0.007, 0.13, $p = 0.03$) (Fig. 3a). For this group, the effect size increased as the treatment duration increased. To check whether the subgroup effect was not due to a type I error we also performed a subgroup analysis and calculated the significance of group by duration interaction. This analysis yielded a significant interaction (z = 2.2, slope = 0.07, CI = 0.007, 0.13, $p = 0.03$).

When the medication group was examined separately, we found that the rate of relapse rate was greater as the double-blind phase is increased (z = 2.40, slope = 0.011, CI = 0.002, 0.02, $p = 0.02$; Fig. 3b). When the three groups were separately examined, we observed that this effect was only significant for the SSRI group (z = 2.70, slope = 0.02, CI = 0.005, 0.03, $p = 0.007$, Fig. 3c). There was no association between the relapse rate and the open phase duration.

When we only examined the relapse event rate in the placebo group, we similarly found a significant effect of double-blind duration on relapse rate (z = 2.4, slope = 0.012, CI = 0.002, 0.024, $p = 0.02$). On the other hand, examining the individual antidepressant groups for the same regression did not reveal any significant effect. Additionally, the effect of open-phase duration on relapse rate was highly significant for the atypical antidepressant group (z = −6.24, slope = −0.14, CI = −0.19, −0.1, $p < 0.001$, Fig. 3d). The group by duration interaction was also significant showing that the subgroup results was not due to a type I error (z = −3.29, slope = −0.15, CI = −0.23, −0.06, $p = 0.001$).

4. Discussion

The present study extracted 37 RCTs in 5351 records and analyzed the effect sizes of antidepressant treatment over placebo for relapse in MDD. Further, several potential factors were also included to explain relapse. The results confirmed that these medications superior in reducing relapse risk to some extent. In addition, we showed that the treatment duration (i.e., open-label phase) may be associated with the relapse rate particularly for the atypical antidepressants, where a longer treatment duration is associated with a greater effect size. In addition, we specifically observed that, for this group, the relapse rate in the placebo group decreased to very low levels after about 20 weeks of treatment and the implication might be that beyond this period

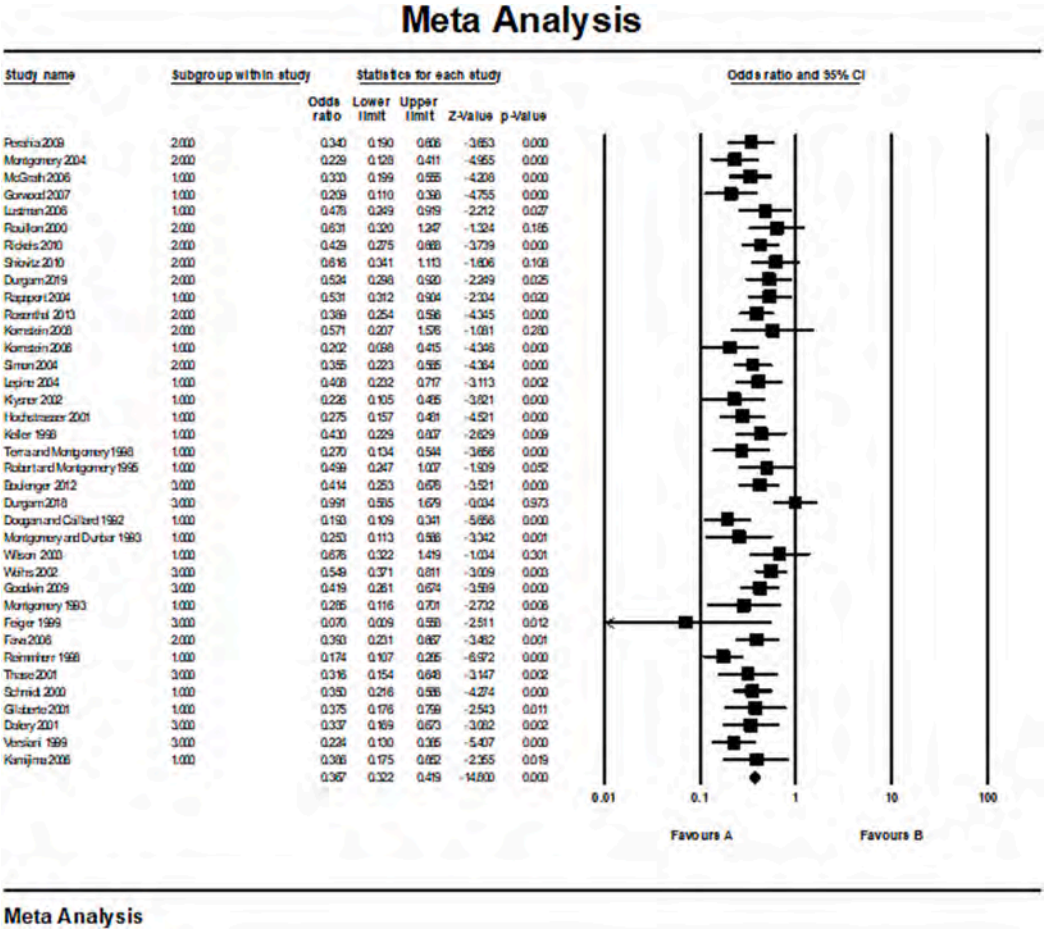

Fig. 2. The forest plot effectiveness of antidepressants versus placebo on relapse rate during follow-up period.

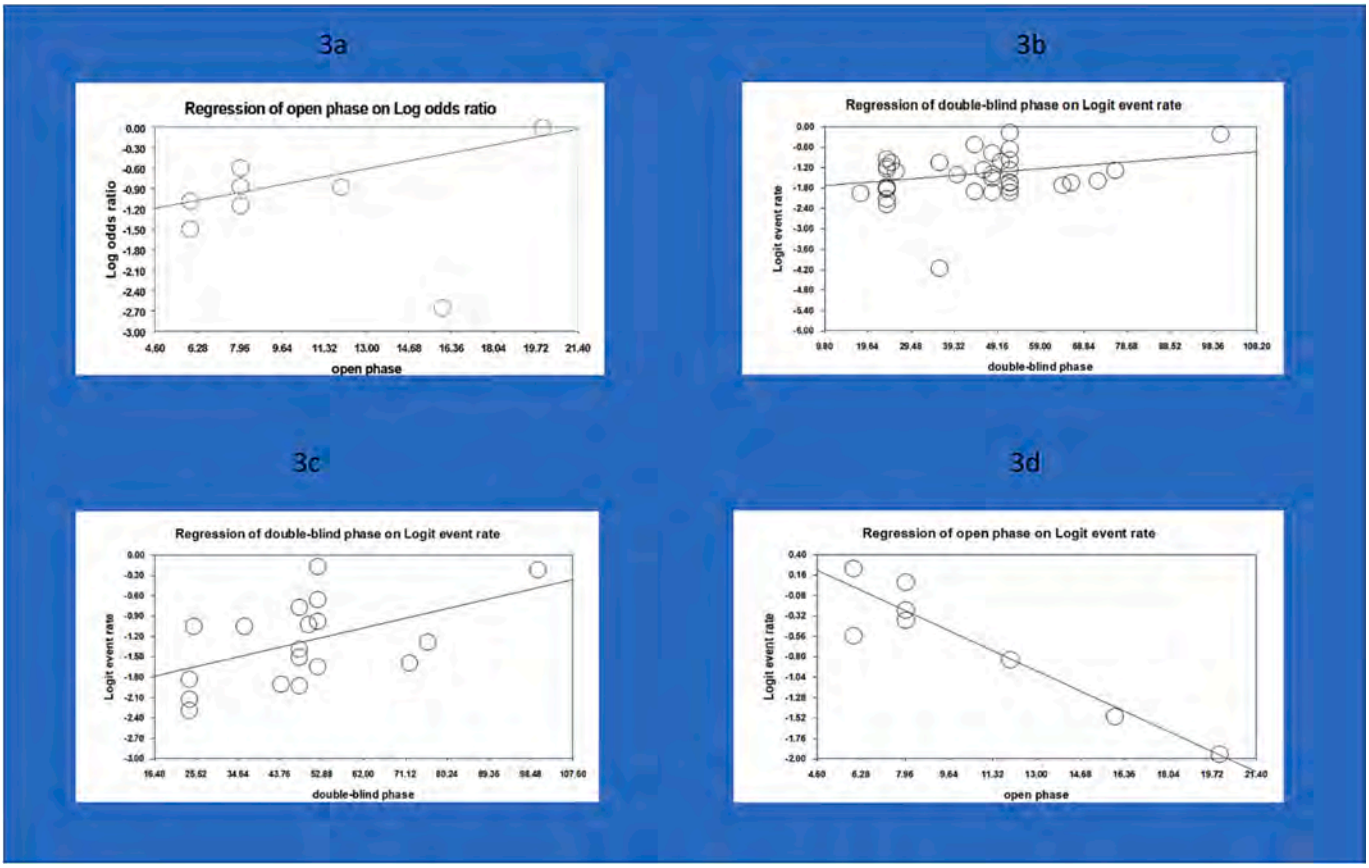

Fig. 3. The meta regression analysis for the effect of duration on effect sizes.
Note: a: The relationship between effect sizes and open-label duration for atypical antidepressants. b: The relationship between effect size and double-blind phase duration-active medication group. c: The relationship between effect size and double-blind phase duration for SSRI studies-active medication group. d: The relationship between effect size and open-label duration for atypical antidepressant studies-placebo group.

excessive exposure to antidepressants may not be necessary as the event rate decreases to a level (%12.5 for Durgam et al., 2018) where the risk of further treatment may outweigh the benefit.

The second important finding our results show is that even though the relapse rate decreases with increased duration, some patients will still experience relapse. To identify such individuals electrophysiological or biochemical markers of relapse could help decision making concerning treatment duration. However, currently the clinicians lack such markers as indicated previously, and we suggest future studies should aim to find markers that will predict relapse risk after treatment discontinuation.

4.1. Strengths and limitations

In this meta-analysis, studies that use the combination of pharmacotherapy and cognitive behavioral therapy were excluded to extract the pure effect of medications. Further, our study also included some newer agents such as levomilnacipran, milnacipran which have a similar effect on MDD as other second-generation ADs (Wagner et al., 2018). Finally, the inclusion of atypical ADs in the analysis revealed the difference in treatment duration effect on relapse. On the other hand, several limitations should be addressed. The exclusion of tricyclic antidepressants (TCAs) could narrow the scope of the meta-analysis, yet TCAs constitute the later steps of MDD treatment due to low safety profiles compared with SSRI, SNRI, and atypical ADs (Wang et al., 2018). Another limitation could be that the longest duration of open-label treatment was 34 weeks, and treatment beyond that period could confer additional protection against relapse. However, this limitation could be overcome in future studies using a longer treatment duration.

5. Conclusion

Despite some reports suggesting certain treatment periods such as 10–12 months (Liu et al., 2021), our meta-analysis indicate that extending the AD use excessively may not confer protection and may expose the patient to unnecessary side effects. It is also worth mentioning that we did observe such an effect in only a subgroup of studies and it is for now not certain if this period could be generalizable to all antidepressants. On the other hand, studying biological, electrophysiological, and genetic markers as predictors of relapse risk in MDD would give promising results. We expect that certain biological markers would be helpful for relapse rates of MDD patients taking SSRI and SNRI treatment. This issue is particularly important given the increasing rate of patients who are on long term anti-depressant treatment. For instance, Luo et al., reported that about that in 2015 about 44 % of depressive patients were using antidepressants for >5 years. According to our results, a majority of these individuals will not experience any relapse or recurrence if they stop using their medication and thus may be unnecessarily exposed to antidepressant medications. Besides, prediction of individuals with a high probability of relapse/recurrence can lead to consideration of sophisticated and intensive treatment options for these individuals. For instance, a recent study reported that combined medication and psychotherapy leads to a higher rate of sustained response as compared to the pharmacotherapy alone in patients with an episode of depression (Furukawa et al., 2021).

In summary, it seems it may not be obligatory to prolonged use of antidepressants (over 2–3 years) for depression as proposed by guidelines (National Collaborating Centre for Mental Health, 2010; Psychological Association, 2019). Since there are no current clinical or

biological markers that may be helpful to decide when to stop medication in the treatment of depression, long-term use is the only way to treat depression as a previous meta-analysis suggests (Kato et al., 2021). However, our conclusion differs from theirs in that since the relapse rate drops significantly in the placebo group with time on treatment, long term use decision may not be beneficial when the overall effect or number needed to treat considered. For individuals with recurrent depression alternative therapeutic strategies to long term continuation of medications include continuation with maintenance psychotherapy (Cosci et al., 2020; Guidi and Fava, 2021).

Role of funding sources

The study did not receive any funding.

CRediT authorship contribution statement

Author 1 designed the research and wrote the protocol. Author 2 and author 3 conducted literature searches and provided full-text articles. Author 2 and author 4 selected eligible studies and extracted data from studies. Author 4 conducted the statistical analysis. Author 2 wrote the first draft of the manuscript and all authors contributed to and have approved the final revised version of the manuscript.

Conflict of interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Acknowledgement

None declared.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596.

Bauer, M., Severus, E., Köhler, S., Whybrow, P.C., Angst, J., Möller, H.J., 2015. In: World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders. Part 2: Maintenance Treatment of Major Depressive Disorder-Update 2015, 16, pp. 76–95. https://doi.org/10.3109/15622975.2014.1001786.

Boulenger, J.P., Loft, H., Florea, I., 2012. A randomized clinical study of lu AA21004 in the prevention of relapse in patients with major depressive disorder. J. Psychopharmacol. 26, 1408–1416. https://doi.org/10.1177/0269881112441866.

Carvalho, A.F., Sharma, M.S., Brunoni, A.R., Vieta, E., Fava, G.A., 2016. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. Psychother. Psychosom. 85, 270–288. https://doi.org/10.1159/000447034.

Cascade, E., Kalali, A.H., Kennedy, S.H., 2009. Real-world data on SSRI antidepressant side effects. Psychiatry (Edgmont) 6, 16.

Clark, S.L., Adkins, D.E., Aberg, K., Hettema, J.M., McClay, J.L., Souza, R.P., van den Oord, E.J.C.G., 2012. Pharmacogenomic study of side-effects for antidepressant treatment options in STAR*D. Psychol. Med. 42, 1151–1162. https://doi.org/10.1017/S003329171100239X.

Cosci, F., Guidi, J., Mansueto, G., Fava, G.A., 2020. Psychotherapy in recurrent depression: efficacy, pitfalls, and recommendations. Expert. Rev. Neurother. 20, 1169–1175. https://doi.org/10.1080/14737175.2020.1804870.

Dalery, J., Dagens-Lafont, V., de Bodinat, C., 2001. Efficacy of tianeptine vs placebo in the long-term treatment (16.5 months) of unipolar major recurrent depression*. Hum Psychopharmacol 16. https://doi.org/10.1002/HUP.269.

Davies, J., Cooper, R.E., Moncrieff, J., Montagu, L., Rae, T., Parhi, M., 2022. The costs incurred by the NHS in England due to the unnecessary prescribing of dependency-forming medications. Addict. Behav. 125, 107143 https://doi.org/10.1016/J.ADDBEH.2021.107143.

Doogan, D.P., Caillard, V., 1992. Sertraline in the prevention of depression. Br. J. Psychiatry 160, 217–222. https://doi.org/10.1192/BJP.160.2.217.

Durgam, S., Chen, C., Migliore, R., Prakash, C., Thase, M.E., 2019. Relapse prevention with levomilnacipran ER in adults with major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. Depress Anxiety 36, 225–234. https://doi.org/10.1002/DA.22872.

Durgam, S., Gommoll, C., Migliore, R., Chen, C., Chang, C.T., Aguirre, M., Thase, M.E., 2018. Relapse prevention in adults with major depressive disorder treated with vilazodone: a randomized, double-blind, placebo-controlled trial. Int. Clin. Psychopharmacol. 33, 304–311. https://doi.org/10.1097/YIC.0000000000000236.

Fava, G.A., Cosci, F., Offidani, E., Guidi, J., 2016. Behavioral toxicity revisited. J. Clin. Psychopharmacol. 36, 550–553. https://doi.org/10.1097/JCP.0000000000000570.

Fava, M., Detke, M.J., Balestrieri, M., Wang, F., Raskin, J., Perahia, D., 2006. Management of depression relapse: re-initiation of duloxetine treatment or dose increase. J. Psychiatr. Res. 40, 328–336. https://doi.org/10.1016/J.JPSYCHIRES.2005.06.005.

Feiger, A.D., Bielski, R.J., Bremner, J., Heiser, J.F., Trivedi, M., Wilcox, C.S., Roberts, D. L., Kensler, T.T., McQuade, R.D., Kaplita, S.B., Archibald, D.G., 1999. Double-blind, placebo-substitution study of nefazodone in the prevention of relapse during continuation treatment of outpatients with major depression. Int. Clin. Psychopharmacol. 14, 19–28. https://doi.org/10.1097/00004850-199901000-00002.

Furukawa, T.A., Shinohara, K., Sahker, E., Karyotaki, E., Miguel, C., Ciharova, M., Bockting, C.L.H., Breedvelt, J.J.F., Tajika, A., Imai, H., Ostinelli, E.G., Sakata, M., Toyomoto, R., Kishimoto, S., Ito, M., Furukawa, Y., Cipriani, A., Hollon, S.D., Cuijpers, P., 2021. Initial treatment choices to achieve sustained response in major depression: a systematic review and network meta-analysis. World Psychiatry : Off. J. World Psychiatric Association (WPA) 20 (3), 387–396. https://doi.org/10.1002/wps.20906.

Gelenberg, A.J., Marlene Freeman, C.P., Markowitz, J.C., Rosenbaum, J.F., Thase, M.E., Trivedi, M.H., van Rhoads, R.S., Reus, V.I., Raymond DePaulo, C.J., Fawcett, J.A., Schneck, C.D., Silbersweig, D.A., 2010. Practice Guideline for the Treatment of Patients With Major Depressive Disorder Third Edition Work Group on Major Depressive Disorder.

Gilaberte, I., Montejo, A.L., de La Gandara, J., Perez-Sola, V., Bernardo, M., Massana, J., Martin-Santos, R., Santiso, A., Noguera, R., Casais, L., Perez-Camo, V., Arias, M., Judge, R., Marcos, M.L., Varona, A., de Dios, A., Blanco, M.L., Lopez-Risueño, J.A., Catarineu, S., Alvarez, E., Puigdemont, D., Domenech, J., Soler, P.A., de Miquel, R., Jorda, L., Elorza, J., Boto, B., Yruretagoyena, B., Coca, E., Ruiz-Zorrilla, M.P., Calatayud, L., Sanchez, P., Huete, T., Hernandez, J., 2001. Fluoxetine in the prevention of depressive recurrences: a double-blind study. J. Clin. Psychopharmacol. 21, 417–424. https://doi.org/10.1097/00004714-200108000-00009.

Goodwin, G.M., Emsley, R., Rembry, S., Rouillon, F., 2009. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 70, 1128–1137. https://doi.org/10.4088/JCP.08M04548.

Gorwood, P., Weiller, E., Lemming, O., Katona, C., 2007. Escitalopram prevents relapse in older patients with major depressive disorder. Am. J. Geriatr. Psychiatry 15, 581–593. https://doi.org/10.1097/01.JGP.0000240823.94522.4C.

Guidi, J., Fava, G.A., 2021. Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder. JAMA Psychiatry 78, 261. https://doi.org/10.1001/jamapsychiatry.2020.3650.

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56.

Hengartner, M.P., 2020. How effective are antidepressants for depression over the long term? A critical review of relapse prevention trials and the issue of withdrawal confounding. Ther. Adv. Psychopharmacol. 10 https://doi.org/10.1177/2045125320921694, 2045125320921694.

Hochstrasser, B., Isaksen, P.M., Koponen, H., Lauritzen, L., Mahnert, F.A., Rouillon, F., Wade, A.G., Andersen, M., Pedersen, S.F., de Swart, J.C.G., Nil, R., 2001. Prophylactic effect of citalopram in unipolar, recurrent depression: placebo-controlled study of maintenance therapy. Br. J. Psychiatry 178, 304–310. https://doi.org/10.1192/BJP.178.4.304.

Huijbregts, K.M., Hoogendoorn, A.W., Slottje, P., van Balkom, A.J.L.M., Batelaan, N.M., 2017. Long-term and short-term antidepressant use in general practice: data from a large cohort in the Netherlands. Psychother. Psychosom. 86, 362–369. https://doi.org/10.1159/000480456.

Kamijima, K., Burt, T., Cohen, G., Arano, I., Hamasaki, T., 2006. A placebo-controlled, randomized withdrawal study of sertraline for major depressive disorder in Japan. Int. Clin. Psychopharmacol. 21 (1), 1–9. https://doi.org/10.1097/01.yic.0000182118.57510.d1.

Kato, M., Hori, H., Inoue, T., Iga, J., Iwata, M., Inagaki, T., Shinohara, K., Imai, H., Murata, A., Mishima, K., Tajika, A., 2021. Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: a systematic review and meta-analysis. Mol. Psychiatry 26, 118–133. https://doi.org/10.1038/S41380-020-0843-0.

Keller, M.B., Kocsis, J.H., Thase, M.E., Gelenberg, A.J., Rush, A.J., Koran, L., Schatzberg, A., Russell, J., Hirschfeld, R., Klein, D., McCullough, J.P., Fawcett, J.A., Kornstein, S., LaVange, L., Harrison, W., 1998. Maintenance phase efficacy of sertraline for chronic depression: a randomized controlled trial. JAMA 280, 1665–1672. https://doi.org/10.1001/JAMA.280.19.1665.

Kennedy, S.H., Lam, R.W., McIntyre, R.S., Tourjman, S.V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A.J., MacQueen, G.M., McInerney, S.J., McIntosh, D., Milev, R.V., Müller, D.J., Parikh, S.V., Pearson, N.L., Ravindran, A.V., Uher, R., 2016. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical

guidelines for the management of adults with major depressive disorder: section 3. Pharmacological treatments. Canadian Journal of Psychiatry 61, 540–560. https://doi.org/10.1177/0706743716659417.
Klysner, R., Bent-Hansen, J., Hansen, H.L., Lunde, M., Pleidrup, E., Poulsen, D.L., Andersen, M., Petersen, H.E.H., 2002. Efficacy of citalopram in the prevention of recurrent depression in elderly patients: placebo-controlled study of maintenance therapy. Br. J. Psychiatry 181, 29–35. https://doi.org/10.1192/BJP.181.1.29.
Kornstein, S.G., Bose, A., Li, D., Saikali, K.G., Gandhi, C., 2006. Escitalopram maintenance treatment for prevention of recurrent depression: a randomized, placebo-controlled trial. J. Clin. Psychiatry 67, 1767–1775. https://doi.org/10.4088/JCP.V67N1115.
Kornstein, S.G., Kocsis, J.H., Ahmed, S., Thase, M., Friedman, E.S., Dunlop, B.W., Yan, B., Pedersen, R., Ninan, P.T., Li, T., Keller, M., 2008. Assessing the efficacy of 2 years of maintenance treatment with venlafaxine extended release 75–225 mg/day in patients with recurrent major depression: a secondary analysis of data from the PREVENT study. Int. Clin. Psychopharmacol. 23, 357–363. https://doi.org/10.1097/YIC.0B013E328314E2CB.
Lépine, J.P., Caillard, V., Bisserbe, J.C., Troy, S., Hotton, J.M., Boyer, P., 2004. A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. Am. J. Psychiatry 161, 836–842. https://doi.org/10.1176/APPI.AJP.161.5.836.
Liu, X., Momen, N.C., Molenaar, N., Rommel, A.S., Bergink, V., Munk-Olsen, T., 2021. Discontinuation of antidepressants: is there a minimum time on treatment that will reduce relapse risk? J. Affect. Disord. 290, 254–260. https://doi.org/10.1016/J.JAD.2021.04.045.
Lustman, P.J., Clouse, R.E., Nix, B.D., Freedland, K.E., Rubin, E.H., McGill, J.B., Williams, M.M., Gelenberg, A.J., Ciechanowski, P.S., Hirsch, I.B., 2006. Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Arch. Gen. Psychiatry 63, 521–529. https://doi.org/10.1001/ARCHPSYC.63.5.521.
Malhi, G.S., Bell, E., Bassett, D., Boyce, P., Bryant, R., Hazell, P., Hopwood, M., Lyndon, B., Mulder, R., Porter, R., Singh, A.B., Murray, G., 2021. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust. N. Z. J. Psychiatry 55, 7–117. https://doi.org/10.1177/0004867420979353.
Mark, T.L., Joish, V.N., Hay, J.W., Sheehan, D.V., Johnston, S.S., Cao, Z., 2011. Antidepressant use in geriatric populations: the burden of side effects and interactions and their impact on adherence and costs. Am. J. Geriatr. Psychiatry 19, 211–221. https://doi.org/10.1097/JGP.0B013E3181F1803D.
Mars, B., Heron, J., Kessler, D., Davies, N.M., Martin, R.M., Thomas, K.H., Gunnell, D., 2017. Influences on antidepressant prescribing trends in the UK: 1995–2011. Soc. Psychiatry Psychiatr. Epidemiol. 52, 193–200. https://doi.org/10.1007/S00127-016-1306-4/FIGURES/5.
McGrath, P.J., Stewart, J.W., Quitkin, F.M., Chen, Y., Alpert, J.E., Nierenberg, A.A., Fava, M., Cheng, J., Petkova, E., 2006. Predictors of relapse in a prospective study of fluoxetine treatment of major depression. Am. J. Psychiatry 163, 1542–1548. https://doi.org/10.1176/AJP.2006.163.9.1542.
Meijer, W.E.E., Heerdink, E.R., Leufken, H.G.M., Herings, M.C., Egberts, A.C.G., Nolen, W.A., 2004. Incidence and determinants of long-term use of antidepressants. Eur. J. Clin. Pharmacol. 60 (1), 57–61. https://doi.org/10.1007/S00228-004-0726-3.
Montgomery, S.A., Dunbar, G., 1993. Paroxetine is better than placebo in relapse prevention and the prophylaxis of recurrent depression. Int. Clin. Psychopharmacol. 8, 189–196. https://doi.org/10.1097/00004850-199300830-00009.
Montgomery, S.A., Entsuah, R., Hackett, D., Kunz, N.R., Rudolph, R.L., 2004. Venlafaxine versus placebo in the preventive treatment of recurrent major depression. J. Clin. Psychiatry 65, 328–336. https://doi.org/10.4088/JCP.V65N0307.
Montgomery, S.A., Rasmussen, J.G.C., Tanghøj, P., 1993. A 24-week study of 20 mg citalopram, 40 mg citalopram, and placebo in the prevention of relapse of major depression. Int. Clin. Psychopharmacol. 8, 181–188. https://doi.org/10.1097/00004850-199300830-00008.
National Collaborating Centre for Mental Health, 2010. Depression: the nice guideline on the treatment and management of depression in adults. Economist 705.
OECD, 2021. Health at a Glance 2021. OECD. https://doi.org/10.1787/ae3016b9-en.
Papanicolas, I., Woskie, L.R., Jha, A.K., 2018. Health care spending in the United States and other high-income countries. JAMA 319, 1024–1039. https://doi.org/10.1001/JAMA.2018.1150.
Perahia, D.G.S., Maina, G., Thase, M.E., Spann, M.E., Wang, F., Walker, D.J., Detke, M.J., 2009. Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 70, 706–716. https://doi.org/10.4088/JCP.08M04756.
Psychological Association A, 2019. APA Clinical Practice Guideline for the Treatment of Depression Across Three Age Cohorts Guideline Development Panel for the Treatment of Depressive Disorders Approved by APA Council of REPRESENTATIVES.
Rapaport, M.H., Bose, A., Zheng, H., 2004. Escitalopram continuation treatment prevents relapse of depressive episodes. J. Clin. Psychiatry 65, 44–49. https://doi.org/10.4088/JCP.V65N0107.
Reimherr, F.W., Amsterdam, J.D., Quitkin, F.M., Rosenbaum, J.F., Fava, M., Zajecka, J., Beasley, C.M., Michelson, D., Roback, P., Sundell, K., 1998. Optimal length of continuation therapy in depression: a prospective assessment during long-term fluoxetine treatment. Am. J. Psychiatry 155, 1247–1253. https://doi.org/10.1176/AJP.155.9.1247.
Rickels, K., Montgomery, S.A., Tourian, K.A., Guelfi, J.D., Pitrosky, B., Padmanabhan, S. K., Germain, J.M., Leurent, C., Brisard, C., 2010. Desvenlafaxine for the prevention of relapse in major depressive disorder: results of a randomized trial. J. Clin. Psychopharmacol. 30, 18–24. https://doi.org/10.1097/JCP.0B013E3181C94C4D.
Robert, P.H., Montgomery, S.A., 1995. Citalopram in doses of 20–60 mg is effective in depression relapse prevention: a placebo-controlled 6 month study. Int. Clin. Psychopharmacol. 10, 29–36. https://doi.org/10.1097/00004850-199503001-00006.
Rosenthal, J.Z., Boyer, P., Vialet, C., Hwang, E., Tourian, K.A., 2013. Efficacy and safety of desvenlafaxine 50 mg/d for prevention of relapse in major depressive disorder:a randomized controlled trial. J. Clin. Psychiatry 74, 158–166. https://doi.org/10.4088/JCP.12M07974.
Rouillon, F., Warner, B., Pezous, N., Bisserbe, J.C., Agussol, P., Alaix, C., Alary, P., Autheman, B., Azra, R., Barbier, D., Baudrillard, C., Bellot, J.C., Benssoussan, M., Bensussan, P., Berdah, C.S., Bessuges, J.M., Billion, A., Blanchard, C., Blauwblomme, J.F., Bonnafoux, D., Bornstein, S., Bouadjera, P., Boubli, S., Bourg, M., Braconnier, A., Brousse, A.M., Burnat, G., Capdeville, Ch., Capdeville, Cl, Cardot, H., Carrier, C.G., Cayssials, P., Charbaut, J., Chelias, A., Clerc, G., Conraux, Costeja, J.M., Cournac, P., Cyran, S., Dabert-Bourasset, M., Danan, A., Danic, M., Daurignac, M., de Nuce De Lamothe, P., Degrais, D., Demant, J.C., Demogeot, C., Depierre, C., Deyrieux, B., Dumon, P.H., Dumont, P., Dussartre, J., Emery, B., Estrabol, Fabiani, J.M., Faruch, M., Ferrey, G., Fonvieille, V., Fuseau, Y., Gandois, F., Gaubert, R., Gaussares, C., Gillard, M.H., Giraud D'Elloy, E., Gozlan, G., Grimaud, B., Grivois, H., Guibert, M., Guilloux, J., Hakim, Hanus, M.Haumonte, Henry, E., Hirigoyen, M.F., Jammes, P., Kalck, M., Kurc, H., Lanvin, F., Laqueille, X., Lavaud, J. L., MT, le Goues, G., Leclercq, P., Lefebvre, P., Legoubey, P., Lermuzeaux, C., Lhoste, Liegaut, D., Lombertie, E.R., Mabillon, M., Magnan, M., Maloux, H., Maquet, D., Marcou, G., Marmin, P., Marro, G., Mathieru, P., May, J.P., Meaux, J.P., Mella, P., 2000. Milnacipran efficacy in the prevention of recurrent depression: a 12-month placebo-controlled study. Milnacipran recurrence prevention study group. Int Clin Psychopharmacol 15, 133–140. https://doi.org/10.1097/00004850-200015030-00002.
Schmidt, M.E., Fava, M., Robinson, J.M., Judge, R., 2000. The efficacy and safety of a new enteric-coated formulation of fluoxetine given once weekly during the continuation treatment of major depressive disorder. J. Clin. Psychiatry 61, 851–857. https://doi.org/10.4088/JCP.V61N1107.
Shiovitz, T., Greenberg, W.M., Chen, C., Forero, G., Gommoll, C.P., 2014. A randomized, double-blind, placebo-controlled trial of the efficacy and safety of levomilnacipran ER 40–120mg/day for prevention of relapse in patients with major depressive disorder. Innov. Clin. Neurosci. 11, 10.
Shrank, W.H., Rogstad, T.L., Parekh, N., 2019. Waste in the US health care system: estimated costs and potential for savings. JAMA 322, 1501–1509. https://doi.org/10.1001/JAMA.2019.13978.
Simon, J.S., Aguiar, L.M., Kunz, N.R., Lei, D., 2004. Extended-release venlafaxine in relapse prevention for patients with major depressive disorder. J. Psychiatr. Res. 38, 249–257. https://doi.org/10.1016/J.JPSYCHIRES.2003.10.004.
Terra, J.L., Montgomery, S.A., 1998. Fluvoxamine prevents recurrence of depression: results of a long-term, double-blind, placebo-controlled study. Int. Clin. Psychopharmacol. 13, 55–62. https://doi.org/10.1097/00004850-199803000-00001.
Thase, M.E., Nierenberg, A.A., Keller, M.B., Panagides, J., 2001. Efficacy of mirtazapine for prevention of depressive relapse: a placebo-controlled double-blind trial of recently remitted high-risk patients. J. Clin. Psychiatry 62, 782–788. https://doi.org/10.4088/JCP.V62N1006.
The Management of Major Depressive Disorder Working Group, 2016. VA/DoD Clinical Practice Guideline for The Management of Major Depressive Disorder.
Versiani, M., Mehilane, L., Gaszner, P., Arnaud-Castiglioni, R., 1999. Reboxetine, a unique selective NRI, prevents relapse and recurrence in long-term treatment of major depressive disorder. J. Clin. Psychiatry 60, 400–406. https://doi.org/10.4088/JCP.V60N0610.
Wagner, G., Schultes, M.-T., Titscher, V., Teufer, B., Klerings, I., Gartlehner, G., 2018. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: a systematic review and network meta-analysis. J. Affect. Disord. 228, 1–12. https://doi.org/10.1016/j.jad.2017.11.056.
Wang, S.-M., Han, C., Bahk, W.-M., Lee, S.-J., Patkar, A.A., Masand, P.S., Pae, C.-U., 2018. Addressing the side effects of contemporary antidepressant drugs: a comprehensive review. Chonnam. Med. J. 54, 101. https://doi.org/10.4068/CMJ.2018.54.2.101.
Weihs, K.L., Houser, T.L., Batey, S.R., Ascher, J.A., Bolden-Watson, C., Donahue, R.M.J., Metz, A., 2002. Continuation phase treatment with bupropion SR effectively decreases the risk for relapse of depression. Biol. Psychiatry 51, 753–761. https://doi.org/10.1016/S0006-3223(01)01317-8.
Wilson, K.C.M., Mottram, P.G., Ashworth, L., Abou-Saleh, M.T., 2003. Older community residents with depression: long-term treatment with sertraline. Randomised, double-blind, placebo-controlled study. Br. J. Psychiatry 182, 492–497. https://doi.org/10.1192/BJP.182.6.492.