ORIGINAL ARTICLE

Analysis of the Pharmacological Management of Major Depressive Disorder in 100 Consecutive Psychiatric Referrals from Two Family Practice Locations in Rural Canada

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ABSTRACT

Background: As the rates of Major Depressive Disorder (MDD) continue to climb in industrialized nations, primary-care providers (PCPs) will continue to treat the majority of people suffering from mood disorders. This analysis reviewed the pharmacological management of MDD to look at the educational needs of PCPs as they continue to treat MDD while waiting for specialist consultation. **Methods:** One-hundred consecutive psychiatric consultation requests from two rural Canadian family practices were analyzed to determine the most common mental health issues for which assistance was sought. Data from the consultation requests and electronic medical records (EMR) were compiled to examine the prescribing choices for people with MDD in these two practices. **Results:** Sixty-eight percent of the consultation requests were for help in managing people with depressive symptoms or MDD, making it the most common condition for which assistance was sought. The most common antidepressant choices were (in order): Escitalopram, venlafaxine, and bupropion. Just six of the 68 (8.8%) people referred were taking an adjunct with the antidepressant and five of the 68 (7.4%) were taking antidepressant combinations. Switching antidepressants was the most common strategy for initial non- or partial response, with an average of 1.78 antidepressant medications having been prescribed at the time of the consultation appointment. **Interpretation:** This analysis revealed a strong preference for antidepressant monotherapy as the mainstay of pharmacologic treatment, and antidepressant switches as the primary means of managing initial non- or partial medication response. The potentially advantageous use of antidepressant combinations and adjunctive agents were employed only in a minority of cases. Medication switches did not appear to take in account the various mechanisms of action of different antidepressant classes. There did not appear to be widespread adoption of established MDD treatment algorithms.

Key words: Antidepressants, Clinical decision making, Major depressive disorder, Primary care

INTRODUCTION

Specialist wait times in Canada reached an all-time high in 2020 at just over 22 weeks.[1] Major Depressive Disorder (MDD) has an estimated lifetime prevalence of 11.3% in Canada and is expected to be the leading cause of disability globally by 2030 according to the World Health Organization.[2,5] Published MDD treatment algorithms[3,4] have not been sufficiently helpful at the primary-care level to reduce the requests for specialist consultation for unipolar mood disorders. The rates of MDD keep rising in industrialized nations due to a variety of factors, primarily lifestyle choices or what are known as "diseases of civilization."[6,7] Estimates of the percentage of family practice visits that are primarily for mental health reasons are difficult to obtain, but one U.S. study determined the overall figure to be 20%, generally increasing as people get older.[8]

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Antidepressant monotherapy response and remission rates vary, but one study that continues to stand out for its design and scope is the STAR*D trial.[9] Step One of this study administered citalopram for up to 12 weeks, with a reported response rate (defined as 50% or greater reduction in symptom severity) of 48.6%. However, there are aspects of this finding that bear scrutiny. First, newer evidence suggests that an assessment at the 2–3 week mark is advisable, with a change in treatment strategy being called for if there isn't at least a 20% reduction in symptom severity.[10-12] Two sets of guidelines and an authoritative textbook recommend a maximum of 8 weeks before making a change in treatment.[3,4,13] Next, citalopram was given in doses of up to 60mg/day, which is in excess of the recommended maximum of 40 mg/day.[13] Finally, the way the final results were tabulated has been called into question.[14] Taking these factors into account to arrive at a more accurate response rate is not easily accomplished, but it is reasonable to conclude that the actual response rate would less than the reported 48.6%, meaning that the likelihood of a non-or partial-response is greater than that of seeing a response. Put another way, primary-care provider (PCPs) should expect that antidepressant monotherapy is more likely not to work than it is to be effective.

Part of this result is due to the mechanism of action of most antidepressants, which is reuptake inhibition. Selective-Serotonin Reuptake Inhibitors, which are the most popular first-line medication choices, are indiscriminate agonists for all serotonin receptor subtypes. While stimulation of serotonin$_{1A}$ (5-HT$_{1A}$) receptors is thought to lead to a reduction in depressive and anxious symptoms, stimulation of 5-HT$_{2A}$ and 5-HT$_{2C}$ (as just two examples) is thought to decrease levels of dopamine and norepinephrine, which worsen the clinical response and may cause adverse treatment-emergent events.[15,16]

Antidepressant combinations have been found in some studies to be more beneficial than monotherapy.[17] The CANMAT guidelines from 2016 list five atypical antipsychotics as having Level 1 evidence as adjuncts in helping partial or non-response situations to antidepressants: Aripiprazole, brexpiprazole, olanzapine, quetiapine, and risperidone.[3]

This analysis was completed to get "real world" data on the management plans of PCPs with regard to antidepressant prescription versatility and the use of antidepressant combinations or adjunctive agents in cases of non- or partial response to initial treatment.

METHODS

The author provides psychiatric consultation services to two towns in rural Canada (populations 6000 and 16,000). Neither location has a psychiatrist with an established practice and referrals for psychiatric care are otherwise directed to the nearest general hospital. Monthly time slots are given to the administrator at each location and the PCPs choose which patients they would like to be seen. Referrals are not vetted by the psychiatric consultant before the appointments being assigned. Repeat consultations are permitted at the discretion of the referring PCP. Where this occurred, only the data from the initial consultation was included in the following analysis. All referrals were seen in person (not via video platforms or phone calls).

One hundred consecutive referrals are summarized here, from 14 different PCPs, with a detailed analysis provided for those requested specifically for the presence of depressive symptoms (e.g., "major depressive disorder," "depression," and "depressive symptoms") even if there were other symptoms or conditions mentioned in the consultation request. The author was given access to the clinic electronic medical record (EMR) at both sites to collect data on the referrals.

All but one of the referring physicians was awarded the Certification in Family Medicine (CCFP designation) from the College of Family Physicians of Canada. Both sites have formalized education programs and allow pharmaceutical representatives to visit in person.

RESULTS

Of the one-hundred consecutive referrals, 68 contained a reference to depressive symptoms. A breakdown of the 32 non-depressive symptom consultations requests is as follows [Table 1]:

A demographic summary of the 68 referrals for depressive symptoms appears in Table 2:

Table 3 summarizes the comorbidities or other clinical situations identified along with 68 depressive symptom referrals (some people had multiple symptoms in addition to the depressive ones).

Table 4 summarizes the medications (monotherapy) prescribed at the time of the consultation, along with the mean, median, and modal doses (listed in order of most to least common).

Table 5 summarizes the antidepressant combinations that were being used at the time of consultation, along with the doses being prescribed. There were incomplete EMR data regarding the amount of time people were taking the combination antidepressants, which prevented a fuller summary from being created.

The duration of time on medications for the 63 referrals on antidepressant monotherapy is summarized in Table 6, rounded to the nearest month (4 weeks), with a maximum being set at 52 weeks (even if the person was taking it longer).

The total number of medication trials for the 68 referrals is summarized in Table 7, the average being 1.78 before a consultation was requested.

Table 8 summarizes the medications that were prescribed prior to the consultation request (these were not the active medications at the time of the consult). The doses and length of administration were inconsistently recorded in the EMR, so that data are not included here. Some people had been taking combinations of antidepressants.

Table 9 shows a more complete picture of antidepressant prescribing by combining the active monotherapy and combination treatments, and along with the past medication choices (amalgamating Tables 4, 5, and 8).

Medications chosen as a percentage of total prescriptions are shown in Chart 1.

In six of the 68 referral requests (8.8%), an adjunctive agent was actively being prescribed. Doses were recorded but not the length of administration (the EMR was incomplete). Table 10 summarizes these results for the active use of adjunctive agents.

In four of the 68 (5.9%) referral requests, there had been a prior prescription for an adjunctive agent, but it was discontinued by the time of the consultation. Data from the EMR were incomplete but doses are included where they were available. Table 11 summarizes the prior use of adjunctive agents.

Table 12 summarizes the psychiatric consultant's diagnosis (if MDD was deemed not to be the best explanation for the person's difficulties). In some cases, the principal diagnosis was changed (e.g., to Bipolar Disorder, Persistent Depressive Disorder (Dysthymia), Adjustment Disorder with Depressed Mood, and Bereavement). In other cases, a full diagnostic summary included MDD and conditions (e.g., Panic Disorder) that may be have had an impact on initiating or maintaining the depressive symptoms (e.g., Substance-Related and Addictive Disorders).

Table 1: Non-depressive symptom referrals

Condition or main symptoms	Number of consultation requests
Bipolar disorder	7
Attention-deficit/Hyperactivity disorder	5
Diagnostic clarification	5
Anxiety disorder	4
Multiple symptoms	3
Obsessive-compulsive and related disorders	2
Personality disorder	1
Posttraumatic stress disorder	1
Schizophrenia	1
Sleep-wake disorder	1
Substance-related and addictive disorder	1
Supportive/Brief psychotherapy	1

Table 2: Demographics of referrals for depressive symptoms

Sex/Gender	Number	Average Age
Females (identify as female)	n=43 (63.2%)	Average age=40.3 y
Males (identify as male)	n=25 (36.8%)	Average age=40.7 y

Table 3: Comorbidities of other clinical situations identified along with depressive symptoms at the time of the consultation

Symptoms identified in addition to depressive symptoms	Number
Partial response/Treatment resistance/ Residual symptoms	16
Anxiety symptoms	15
Clarify the diagnosis	6
Other symptoms	4
Substance-related and addictive disorders	3
Anger issues	2
Posttraumatic stress disorder/Symptoms	2
MDD with peripartum onset	1
MDD with seasonal pattern	1

MDD: Major depressive disorder

INTERPRETATION

A summary of the results reveals the following findings:

- The main consultation request regarding people referred for depressive symptoms was for medication advice regarding non- or partial response, indicating uncertainty with how to proceed after the first one or two antidepressant trials
- The dosing of antidepressants was inconsistent. In some cases, doses were used at the top of the recommended range (e.g., citalopram, duloxetine, and sertraline). In other cases, the average dose was suboptimal (e.g., venlafaxine and quetiapine)
- The average time people were taking an antidepressant with suboptimal results was well over half a year (and would have been longer except the data was capped at 52 weeks), indicating a potential lack of awareness of the brain changes that can occur in repeated, severe, prolonged, or partially treated episodes of MDD[18]

Table 4: Most to least common medications (monotherapy) being prescribed at the time of the consultation along with mean, median, and modal doses, n=63

Medication	Number	Mean dose (mg)	Median dose (mg)	Modal dose (mg)
None	15	NA	NA	NA
Escitalopram (Cipralex®)	14	15.71	20	20
Venlafaxine XR (Effexor XR®)	12	168.75	150	150
Citalopram (Celexa®)	4	40	40	40
Paroxetine (Paxil®)	4	37.5	35	NA
Desvenlafaxine (Pristiq®)	3	100	100	100
Duloxetine (Cymbalta®)	3	110	120	120
Sertraline (Zoloft®)	3	166.7	200	200
Bupropion XL (Wellbutrin® XL)	2	225	225	NA
Vortioxetine (Trintellix®)	2	20	20	20
Quetiapine XR (Seroquel® XR)	1	50	50	50

Table 5: Antidepressant combinations and doses, n=5

Medication 1	Medication 1 dose (mg)	Medication 2	Medication 2 dose (mg)
Escitalopram	20	Bupropion XL	150
Escitalopram	20	Bupropion XL	150
Escitalopram	20	Venlafaxine XR	37.5
Duloxetine	90	Bupropion XL	300
Venlafaxine XR	300	Bupropion SR	100

Table 6: Time on antidepressant monotherapy at the time of the consultation (rounded to the nearest month), n=48

Medication	Number	Mean duration (weeks)	Median duration (weeks)	Modal duration (weeks)
Escitalopram (Cipralex®)	14	27.85	26	52
Venlafaxine XR (Effexor XR®)	12	24.16	10	8
Citalopram (Celexa®)	4	45.5	52	52
Paroxetine (Paxil®)	4	45.5	52	52
Desvenlafaxine (Pristiq®)	3	22.67	8	8
Duloxetine (Cymbalta®)	3	36	52	52
Sertraline (Zoloft®)	3	21.33	8	NA
Bupropion XL (Wellbutrin® XL)	2	4	4	4
Vortioxetine (Trintellix®)	2	28	NA	NA
Quetiapine XR (Seroquel® XR)	1	52	52	52

- On average, people were given 1.78 antidepressants, indicating that after one medication switch, the referring PCPs were unclear as to what to do next. Rarely were more than three antidepressants tried, even when the depressive symptoms extended for several months
- Escitalopram, venlafaxine and bupropion made up 50% of the antidepressants chosen. There was scant use of the newer agents or those have unique pharmacological properties or mechanisms of action, such as: levomilnacipran, mirtazapine, vilazodone, and vortioxetine. It did not appear that there was an understanding of what made these medications unique and potentially advantageous in certain clinical situations
- The use of antidepressant combinations and adjunct medications was comparatively low.

Table 7: Total number of medication trials for the 68 patients referred for depressive symptoms

Number of antidepressant trials	Number of patients (total=68)
0	3
1	34
2	15
3	10
4	3
5	3

Table 8: Previous medication trials

Medication	Number of trials
Escitalopram (Ciplralex®)	15
Venlafaxine XR (Effexor® XR)	9
Bupropion XL (Wellbutrin® XL)	8
Citalopram (Celexa®)	8
Desvenlafaxine (Pristiq®)	4
Fluoxetine (Prozac®)	4
Sertraline (Zoloft®)	3
Vortioxetine (Trintellix®)	3
Duloxetine (Cymbalta®)	2
Amitriptyline (Elavil®)	1
Mirtazapine (Remeron®)	1
Paroxetine (Paxil®)	1
Quetiapine (Seroquel®)	1
Vilazodone (Viibryd®)	1

Explanation

There are currently 26 antidepressants available in Canada comprising ten different mechanisms of action.[19] There is presently no reliable means of matching symptoms to an effective antidepressant choice.[20] Current algorithms provide some guidance on initial antidepressant choices and switch vs. adjunct strategies, but this has yet to permeate to a widespread level for PCPs.[3,4]

Future Directions

Educational programs that focus on mechanism of action would help PCPs make more pharmacologically sound medication switches in the event of initial non- or partial response. Further, there is an opportunity for educational programs that look at ways beyond switching antidepressants to increase the chances that pharmacological choices will beneficial, specifically antidepressant combinations and adding adjunctive agents. In the absence of psychiatric specialists developing increased capacity to assess referrals for depressive symptoms, educational programs that give PCPs sound pharmacologic strategies or a "roadmap" to follow when the people they treat for MDD do not see the expected the results from an initial course of an antidepressant are needed. Put another way, the aim such programs should be to give PCPs "other things to try" while waiting for psychiatrists to offer appointment times.

Limitations of the Study

The data for this study were distilled only from the information provided in the consultation request and the EMR. If there were deficiencies in documentation,

Table 9: Summary of active and prior antidepressant choices

Medication	Active monotherapy	Active combination	Past medication trials	Total number (%)
Escitalopram (Ciplralex®)	14	3	15	32 (23.9)
Venlafaxine XR (Effexor® XR)	12	2	9	23 (17.2)
None	15			15 (11.2)
Bupropion SR or XL (Wellbutrin® SR or XL)	2	4	8	14 (10.4)
Citalopram (Celexa®)	4		8	12 (9)
Desvenlafaxine (Pristiq®)	3		4	7 (5.2)
Duloxetine (Cymbalta®)	3	1	2	6 (4.5)
Sertraline (Zoloft®)	3		3	6 (4.5)
Paroxetine (Paxil®)	4		1	5 (3.7)
Vortioxetine (Trintellix®)	2		3	5 (3.7)
Fluoxetine (Prozac®)	0		4	4 (3)
Quetiapine (Seroquel®)	1		1	2 (1.5)
Amitriptyline (Elavil®)	0		1	1 (0.7)
Mirtazapine (Remeron®)	0		1	1 (0.7)
Vilazodone (Viibryd®)	0		1	1 (0.7)
Total number of medication choices				134

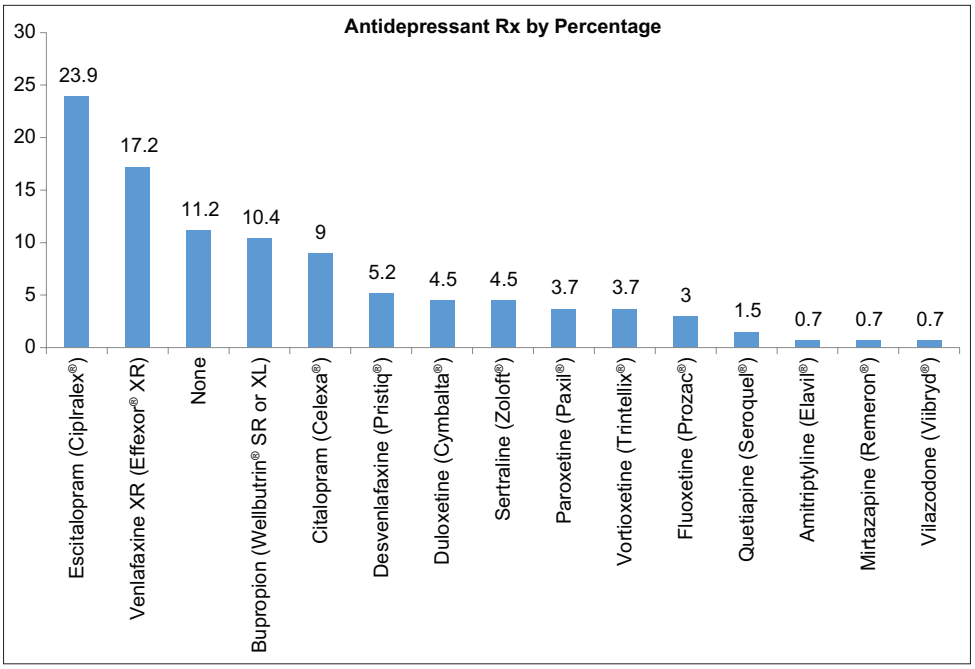

Chart 1: Current and past medications prescribed (134 Total events)

Table 10: Use of adjunctive medications at the time of the consult

Medication	Dosage (mg)
Aripiprazole (Abilify®)	5
Aripiprazole (Abilify®)	4
Aripiprazole (Abilify®)	2
Aripiprazole (Abilify®)	2
Brexpiprazole (Rexulti®)	0.5
Olanzapine (Zyprexa®)	2.5

Table 11: Use of adjunctive medications prior to time of the consult

Medication	Dosage (mg)
Aripiprazole (Abilify®)	5
Brexpiprazole (Rexulti®)	0.5
Risperidone (Risperdal®)	NA
Quetiapine (Seroquel®)	NA

they would have been incorporated into the results. If patients sought treatment from sources other than their usual PCPs, this information would not have been included in the clinic EMR. The effectiveness of non-pharmacological treatments was not possible to evaluate in this study. This data were an analysis of people who were referred for specialist opinion and not those who had been successfully treated.

Table 12: Summary of re-diagnosis or comorbid conditions in the 68 referrals for MDD

Condition	Number
Attention-deficit hyperactivity disorder	12
Bipolar disorder	12
Alcohol use disorder	8
Borderline personality disorder	8
Sleep-wake disorders	7
Posttraumatic stress disorder	5
Social anxiety disorder	4
Panic disorder	3
Personality disorder (Cluster C)	3
Adjustment disorder with depressed mood	2
Bereavement	2
Cannabis use disorder	2
Obsessive-compulsive personality disorder	2
Persistent depressive disorder (Dysthymia)	2
Binge eating disorder	1
Hoarding disorder	1
Histrionic personality disorder	1
Intermittent explosive disorder	1
Major depressive disorder with seasonal pattern	1
Obsessive-compulsive disorder	1
Opioid use disorder	1
Paraphilic disorder	1
Stimulant use disorder	1

MDD: Major depressive disorder

CONCLUSION

PCPs will continue to treat the majority of people with depressive symptoms and MDD and specialist consultation wait times in Canada are likely to continue to lengthen. This analysis reveals opportunities for education that focuses on antidepressant mechanisms of action, rational use of antidepressant combinations, and the use of adjunctive agents to increase the likelihood of successful treatment of MDD.

REFERENCES

1. Waiting your Turn: Wait Times for Health Care in Canada, 2020 Report: Fraser Institute; 2020. Available from: http://www.fraserinstitute.org/studies/waiting-your-turn-wait-times-for-health-care-in-canada-2020#:~:text=The%20total%20wait%20time%20that,when%20it%20was%203.7%20weeks. [Last accessed on 2021 Jan 03].
2. Lam RW, McIntosh D, Wang JL, Enns MW, Kolivakis T, Michalak EE, *et al*. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 1. Disease burden and principles of care. Can J Psychiatry 2016;61:510-23.
3. Kennedy SH, Lam RW, McIntyre RS, Tourjman SV, Bhat V, Blier P, *et al*. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. Can J Psychiatry 2016;61:540-60.
4. 2019-2020 Treatment of adult Major Depressive Disorder. Tampa FL: Florida Center for Behavioral Health Improvement and Solutions, University of South Florida; 2019. Available from: http://www.floridabhcenter.org/2019-2020-treatment-of-adult-major-depressive-disorder.html. [Last accessed on 2021 Jan 03].
5. World Health Organization. The Global Burden of Disease, 2004 Update. Geneva: World Health Organization; 2008. Available from: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en. [Last accessed 2021 Jan 03].
6. Hidaka BH. Depression as a disease of modernity: explanations for increasing prevalence. J Affect Dis 2012;140:205-14.
7. Reddit, Facebook, Twitter Worst for Mental Health Post-coronavirus; YouTube Best. Forbes; 2020. Available from: https://www.forbes.com/sites/johnkoetsier/2020/04/26/reddit-worst-for-mental-health-for-covid-19-news-consumption-survey-says/?sh=432bf40531cf. [Last accessed on 2021 Jan 03].
8. Olfson M, Kroenke K, Wang S, Blanco C. Trends in office-based mental health care provided by psychiatrists and primary care physicians. J Clin Psychiatry 2014;75:247-53.
9. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, *et al*. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am J Psychiatry 2006;163:1905-17.
10. Szegedi A, Müller MJ, Anghelescu I, Klawe C, Kohnen R, Benkert O. Early improvement under mirtazapine and paroxetine predicts later stable response and remission with high sensitivity in patients with major depression. J Clin Psychiatry 2003;64:413-20.
11. Szegedi A, Jansen WT, van Willigenburg AP, van der Meulen E, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: A meta-analysis including 6562 patients. J Clin Psychiatry 2009;70:344-53.
12. Henkel V, Seemüller F, Obermeier M, Adli M, Bauer M, Mundt C, *et al*. Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. J Affect Disord 2009;115:439-49.
13. Stahl SM. Prescriber's Guide. 6th ed. Cambridge UK: Cambridge University Press; 2017.
14. Pigott HE. The STAR*D trial: It is time to reexamine the clinical beliefs that guide the treatment of major depression. Can J Psychiatry 2015;60:9-13.
15. Blier P, Blondeau C. Neurobiological bases and clinical aspects of the use of aripiprazole in treatment-resistant major depressive disorder. J Affect Dis 2011;128S1:S3-10.
16. Blier P, El Mansari M. Serotonin and beyond: Therapeutics for major depression. Philos Trans R Soc Lond B Biol Sci. 2013;368:20120536.
17. Blier P, Ward HE, Tremblay P, Laberge L, Hébert C, Bergeron R. Combination of antidepressant medications from treatment initiation for major depressive disorder: A double-blind randomized study. Am J Psychiatry 2010;167:281-8.
18. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: A 3-year prospective study. Psychol Med 2011;41:1165-74.
19. Procyshyn RM, Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Clinical Handbook of Psychotropic Drugs. 23rd ed. Boston MA: Hogrefe Publishing; 2019.
20. Arnow BA, Blasey C, Williams LM, Palmer DM, Rekshan W, Schatzberg AF, *et al*. Depression subtypes in predicting antidepressant response: A report from the iSPOT-D trial. Am J Psychiatry 2015;172:743-50.

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