Response and Discontinuation Rates of Newer Antidepressants: A Meta-Analysis of Randomized Controlled Trials in Treating Depression

MANIT SRISURAPANONT, M.D.*

Abstract

Several attempts to improve antidepressants have recently led to the availability of some newer antidepressants (NAs) including nefazodone, mirtazapine, and venlafaxine. The author proposed to compare both efficacy and discontinuation rates between these NAs and older antidepressants (OAs) which include tricyclic antidepressants (TCAs), nontricyclic antidepressants (NTCAs), and selective serotonin reuptake inhibitors (SSRIs). In each comparison, the author analyzed the heterogeneity of outcomes and computed the pooled odd ratio (OR) with 95 per cent confidential interval (95% CI) by using Peto method. The results show that NAs have slightly higher efficacy than OAs. The overall discontinuation rate of the NA group was also lower than that of the TCA group but not that of NTCA-SSRI group. In conclusion, NAs have slightly but significantly superior efficacy to OAs which probably include SSRIs. They are also more tolerable than TCAs but not NTCAs-SSRIs. However, the efficacy difference between NAs and SSRIs should be viewed as a preliminary result since very few studies have compared their efficacy.

The existing antidepressants are not completely satisfactory. About one-fourth to one-third of depressed patients do not respond to or can not tolerate them. Selective serotonin reuptake inhibitors (SSRIs), once considered as a breakthrough of antidepressant development, are also not much better than those presented before. In comparison to tricyclic antidepressants (TCAs) and nontricyclic antidepressants (NTCAs), SSRIs are equi-effective[1] and is slightly more tolerable than TCAs[2-4].

Several attempts to improve antidepressants have recently led to the availability of some newer antidepressants (NAs) including nefazodone, mirtazapine, and venlafaxine. These NAs do not have severe adverse effects because they mainly act only on the receptors responsible for relief depression. In addition to the ability to increase serotonin activity, venlafaxine and mirtazapine can enhance noradrenergic activity[5,6], and nefazodone has 5-HT2 antigonistic effect[7]. The wider-ranging thera-

* Department of Psychiatry, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand.

peutic actions and few adverse effects of these NAs differ from those of older antidepressants (OAs) which are TCAs, NTCAs, and SSRIs. The author, therefore, proposed to examine the differences of NAs and OAs in regard to response and discontinuation rates.

MATERIAL AND METHOD

NAs included in the present meta-analysis are only nefazodone, mirtazapine, and venlafaxine since very little evidence can be found with others. The author performed MEDLINE search to detect the randomized controlled trials (RCTs) of nefazodone, mirtazapine, or venlafaxine studies and found 38 articles between 1989 and 1996. Of these, 13 articles presented the response and/or discontinuation rates of both NAs and OAs including 8 nefazodone studies[8-15], 3 venlafaxine studies[16-18], 2 mirtazapine studies[19,20]. Owing to the failure of electronic searches to detect all relevant references, the author also examined the published reference lists of detected articles and found 1 nefazodone and 1 mirtazapine studies[21,22]. Since the article of Rickels et al (1995) reported 4 trials, all 15 articles presented 18-trial results.

The meta-analysis of efficacy was performed on an intent-to-treat basis. The response rate was computed by using the number of responders (rated at least 50 per cent reduction of the score of Hamilton Depression Rating Scale (HDRS) or less than 3 of the Clinical Global Impression (CGI) Scale on last visits) as the numerator and the number of total subjects (being evaluated at least once in the trial) as the denominator. Where the numbers of both HDRS and CGI responders were presented, priority was given to the number of HDRS responders. Since several factors affect patient's dropping out of psychiatric treatments[2,23], only the discontinuation rates due to the lack of efficacy or adverse effects were concerned. These discontinuation rates were calculated by using the number of drop-outs as the numerator and the number of total subjects at entry as the denominator.

Odd ratio (OR) with 95 per cent confidential interval (95% CI) was computed for each rate comparison[24,25]. A separate meta-analysis was carried out for each of the overall comparison between NA and OA response rates, the overall comparison between NA and TCA discontinuation rates, and the overall comparison between NA and NTCA-SSRI discontinuation rates. The separation was based on the fact that no efficacy difference among OAs has been found and NTCA-SSRIs are more tolerable than TCAs. In each overall comparison, the author analyzed the heterogeneity of outcomes and computed the pooled OR with 95 per cent CI by using Peto method[26].

RESULTS

All included trials were carried out in major depressive patients for 6-8 weeks. Of 18 trials, 12 were placebo-controlled studies. Lack of the intent-to-treat response rates in a study caused the inclusion of 17-trial results in the heterogeneity analysis of the compared NA and OA response rates. As 5 trials had not reported TCA discontinuation rate, only 8-trial discontinuation rates were included in the heterogeneity analysis of the compared NA and TCA discontinuation rates. Five trials left were included in the heterogeneity analysis of the compared NA and NTCA-SSRI discontinuation rates. Note that low-dose nefazodone data presented in the 2 trials were not included in the present meta-analysis[9,10]. The characteristics of each trial are presented in Table 1.

OR (95% CI) of each comparison is presented in Table 2. Of 18 trials, Feighner et al and Ansseau et al had given nefazodone only in low dose (mean 180 mg/day and 242 mg/day, respectively). The author excluded these studies for two reasons. First, the results of Fontain's study had shown that low-dose nefazodone (mean 242 mg/day) was significantly less effective than a therapeutic-dose of nefazodone (mean 460 mg/day). Second, the inclusion of these studies caused the significant heterogeneity of the compared NA and TCA discontinuation rates (χ^2 = 18.11; df = 7; p = 0.01) and the heterogeneity trend of the compared NA and OA response rates (χ^2 = 22.74; df = 16; p = 0.12). The exclusion of these two studies led to the homogenous outcome of the compared NA and OA response rates (χ^2 = 10.44; df = 14; p = 0.73), the compared NA and TCA discontinuation rates (χ^2 = 4.43; df = 5; p = 0.49), and the compared NA and NTCA-SSRI discontinuation rates (χ^2 = 5.54; df = 4; p = 0.24).

Of 1889 patients included in the overall comparison of NA and OA response rates, 606 of 942 NA patients and 553 of 947 OA patients responded to the given treatment. The significant higher response rate of NA group was shown by the pooled OR (95% CI) of 1.29 (1.07 to 1.55).

Table 1. Characteristics of the trials included in the separate meta-analysis of response and discontinuation rates between newer antidepressants and older antidepressants.

Author	Study Design[a]	Dx[b]	Study Duration (weeks)	NA, Mean Dose (mg/day)[c]	OA, Mean Dose (mg/day)[d]
Feighner et al. 1989	DB, PC	MD (DSM-III and RDC)	6	NEF, 180	IMI, 158
Smith et al. 1990	DB, PC	MD (DSM-III)	6	MIR, 18	AMI, 111
Cunningham et al. 1994	DB, PC	MD (DSM-III-R)	6	VEN, 297	TRA, 159
Schweizer et al. 1994	DB, PC	MD (DSM-III-R)	6	VEN, 179	IMI, 170
Fontaine et al. 1994	DB, PC	MD (RDC)	6	NEF, 460	IMI, 214
Rickels et al. 1994	DB, PC	MD (DSM-III-R)	8	NEF, 375	IMI, 174
Clerc et al. 1994	DB	MD with melancholia (DSM-III-R)	6	VEN, 200	FLU, 40
Ansseau et al. 1994	DB	MD (DSM-III-R)	6	NEF, 242	AMI, 124
van Moffaert et al. 1995[e]	DB	MD (DSM III)	6	MIR, N/A	TRA, N/A
Rickels et al. 1995 (1)	DB, PC	MD (DSM-III-R or RDC)	6	NEF, 460	IMI, 214
Rickels et al. 1995 (2)	DB, PC	MD (DSM-III-R or RDC)	8	NEF, 375	IMI, 174
Rickels et al. 1995 (3)	DB, PC	MD (DSM-III-R or RDC)	8	NEF, 419	IMI, 176
Rickels et al. 1995 (4)	DB, PC	MD (DSM-III-R or RDC)	8	NEF, 332	IMI, 148
Bremmer et al. 1995	DB, PC	MD (DSM-III)	6	MIR, 22	AMI, 133
Zivkov et al. 1995	DB	MD (DSM III and RDC)	6	MIR, 52.8	AMI, 197
Cohn et al. 1996	DB, PC	MD (DSM-III-R)	8	NEF, 321	IMI, 126
Baldwin et al. 1996	DB	MD (DSM-III-R)	8	NEF, 472	PAR, 32.7
Feiger et al. 1996	DB	MD (DSM-III-R)	6	NEF, 456	SER, 148

[a] DB = double-blind; PC = placebo-controlled.
[b] MD = major depression; DSM = diagnostic and statistical manual; RDC = research diagnostic criteria.
[c] NEF = nefazodone; MIR = mirtazapine; VEN = venlafaxine.
[d] IMI = imipramine; AMI = amitriptyline; TRA = trazodone; FLU = fluoxetine; PAR = paroxitine; SER = sertaline.
[e] Endpoint mean doses are not available, but the endpoint dose ranges of mirtazapine and trazodone are 24-72 mg/day and 150-45 mg/day, respectively.

Table 2. The response-rate odd ratio (95%CI) and the discontinuation-rate odd ratio (95%CI) of each rate comparison*

Author	Responders/Total of		Drop-outs/Total of		Response-Rate Odd Ratio (95% CI)	Discontinuation-Rate Odd Ratio (95%CI)
	NA group	OA group	NA group	OA group		
Feighner et al. 1989	10/15	8/15	1/15	5/15	1.75 (-0.84 to 4.34)	0.14 (-0.18 to 0.47)
Smith et al. 1990	25/47	26/47	N/A	N/A	0.92 (0.17 to 1.66)	N/A
Cunningham et al. 1994	47/65	43/71	16/72[b]	21/77[b]	1.70 (0.47 to 2.93)	0.76 (0.19 to 1.33)
Schweizer e t al 1994	49/64	43/71	15/73[a]	19/73[a]	2.13 (0.53 to 3.72)	0.74 (0.17 to 1.30)
Fontaine et al. 1994	25/44	22/45	6/44[a]	17/45[a]	1.38 (0.23 to 2.52)	0.26 (-0.01 to 0.53)
Rickels et al. 1994	N/A	N/A	14/96[a]	29/92[a]	N/A	0.37 (0.11 to 0.64)
Clerc et al. 1994	24/33	17/34	4/34[b]	11/34[b]	2.67 (-0.05 to 5.39)	0.28 (-0.07 to 0.63)
Ansseau et al. 1994	21/55	34/51	17/55	6/51	0.31 (0.06 to 0.56)	3.36 (-0.09 to 6.80)
van Moffaert et al. 1995	61/100	51/100	18/100[b]	18/100[b]	1.50 (0.66 to 2.35)	1.00 (0.28 to 1.72)
Rickels et al. 1995 (1)	31/50	29/50	N/A	N/A	1.18 (0.23 to 2.13)	N/A
Rickels et al. 1995 (2)	56/86	44/83	N/A	N/A	1.65 (0.63 to 2.68)	N/A
Rickels et al. 1995 (3)	26/41	26/41	N/A	N/A	1.00 (0.10 to 1.90)	N/A
Rickels et al. 1995 (4)	26/39	24/38	N/A	N/A	1.17 (0.07 to 2.26)	N/A
Bremmer et al. 1995	31/50	24/50	6/50[a]	8/50[a]	1.77 (0.36 to 3.18)	0.72 (-0.10 to 1.53)
Zivkov et al. 1995	80/113	80/111	9/125[a]	11/126[a]	0.94 (0.40 to 1.48)	0.81 (0.07 to 1.56)
Cohn et al. 1996	25/39	23/38	8/39[a]	11/38[a]	1.17 (0.09 to 2.24)	0.63 (-0.03 to 1.30)
Baldwin et al. 1996	58/100	60/96	18/105[b]	14/101[b]	0.83 (0.35 to 1.30)	1.29 (0.31 to 2.26)
Feiger et al. 1996	42/71	41/72	15/78[b]	12/82[b]	1.10 (0.37 to 1.82)	1.39 (0.23 to 2.54)

* Odds ratios of higher than one indicate higher rates of NA group.
[a] Discontinuation rate included in the overall comparison of the discontinuation rates from NAs and TCAs.
[b] Discontinuation rate included in the overall comparison of the discontinuation rates from NAs and NTCA-SSRIs.

Of 851 patients included in the overall comparison of NA and TCA discontinuation rates, 58 of 427 NA patients and 95 of 424 TCA patients dropped out of the given treatment. The significantly lower discontinuation rate of NA group was shown by the pooled OR (95% CI) of 0.54 (0.38 to 0.77).

Of 783 patients included in the overall comparison of NA and NTCA-SSRI discontinuation rates, 71 of 389 NA patients and 76 of 394 NTCA-SSRI patients dropped out of the given treatment. The pooled OR (95% CI) of 0.94 (0.66 to 1.35) showed the nonsignificant difference of NA and NTCA-SSRI discontinuation rates.

DISCUSSION

Since all of the data extracted from 6-8 weeks' studies, any conclusions yielded from the present meta-analysis represent the response and discontinuation rates of NAs only in the acute treatment of major depressive disorder. From the results, NAs are significantly better than TCAs in terms of lower discontinuation rate. In the overall comparison of response rates, the efficacy of NAs is slightly but significantly higher than that of OAs. However, the discontinuation rates of NAs and NTCA-SSRIs do not differ.

The number needed to treat (NNT), equivalent to the reciprocal of the absolute risk increase or reduction[27], can help estimate the magnitude of difference[28], therefore, the main benefits of NAs indicated by NNTs were also assessed. In comparison to OAs, the benefits of NAs are as follows: 1) one of 17 depressed patients replaced OAs with NAs will be switched from nonresponder to responder, 2) one of 12-13 depressed patients replaced TCAs with NAs will not discontinue the given antidepressant by the lack of efficacy or adverse effects.

As SSRIs are first-line treatments for major depressive disorder at present, the lower discontinuation rate of NAs in comparison to TCAs appears to have little impact on our practice. That NAs have superior efficacy to OAs seems to be an important finding in this meta-analysis. Taken together with the finding that SSRIs are not more efficient than TCAs and NTCAs[1], the superior efficacy of NAs found in the present analysis may indicate the superior efficacy of NA to that of SSRIs. However, the efficacy difference between NAs and SSRIs should be viewed as a preliminary result since very few studies have compared their efficacy. More studies with head-to-head comparison between NAs and SSRIs are still needed.

In conclusion, NAs have slight but significantly superior efficacy to OAs which probably include SSRIs. They are also more tolerable than TCAs but not NTCA-SSRIs. However, the efficacy difference between NAs and SSRIs should be viewed as a preliminary result since very few studies have compared their efficacy.

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อัตราการตอบสนองและการหยุดใช้ยาต้านซึมเศร้าชนิดใหม่: มหวิเคราะห์ของการทดลองที่มีการควบคุมและสุ่มตัวอย่างในการรักษาโรคซึมเศร้า

*มานิต ศรีสุรภานนท์, พ.บ.**

ความพยายามที่จะปรับปรุงยาต้านซึมเศร้าในระยะหลังได้นำไปสู่การค้นพบยาต้านซึมเศร้าชนิดใหม่ซึ่งประกอบด้วย nefazodone, mirtazapine และ venlafaxine ผู้นิพนธ์จึงได้ทำการเปรียบเทียบอัตราการตอบสนองและการหยุดใช้ยาระหว่างยาต้านซึมเศร้าชนิดใหม่กับยาต้านซึมเศร้าชนิดเก่าซึ่งประกอบด้วย tricyclic antidepressants (TCAs), nontricyclic antidepressants (NTCAs) และ selective serotonin reuptake inhibitors (SSRIs) ในแต่ละการเปรียบเทียบผู้นิพนธ์ได้วิเคราะห์ความแตกต่างของผลลัพธ์และคำนวณค่า pooled odd ratio (OR) กับ 95% confidence interval (95% CI) โดยใช้วิธีการของ Peto ผลการศึกษาพบว่ายาต้านซึมเศร้าชนิดใหม่มีประสิทธิภาพสูงกว่ายาต้านซึมเศร้าชนิดเก่าเล็กน้อย การหยุดยาในผู้ป่วยที่ได้รับยาต้านซึมเศร้าชนิดใหม่ก็น้อยกว่าผู้ป่วยที่ได้รับ TCAs แต่ไม่น้อยกว่าผู้ป่วยที่ได้รับ NTCAs–SSRIs โดยสรุป ยาต้านซึมเศร้าชนิดใหม่มีประสิทธิภาพสูงกว่ายาต้านซึมเศร้าชนิดเก่าซึ่งอาจรวมถึง SSRIs เล็กน้อย ผู้ป่วยจะทนต่อยาต้านซึมเศร้าชนิดใหม่ได้ดีกว่า TCAs แต่ไม่ดีกว่า NTCAs–SSRIs อย่างไรก็ตามควรคำนึงว่าความแตกต่างของประสิทธิภาพของยาดังกล่าวเป็นเพียงผลขั้นต้นเท่านั้นเนื่องจากยังมีการศึกษาเพื่อเปรียบเทียบประสิทธิภาพของยาต้านซึมเศร้าชนิดใหม่กับ SSRIs น้อยมาก

* ภาควิชาจิตเวชศาสตร์, คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่, จ. เชียงใหม่ 50200