Switching Antidepressants for Treatment-Resistant Major Depression

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A substantial proportion of patients suffering from major depression experience insufficient clinical response, despite appropriate treatment. Switching to a different monotherapy antidepressant medication is the preferred option for many patients and clinicians. The possible advantages of switching to a different monotherapy, as compared with adding a second agent (i.e., augmenting or combining), include reduced medication costs, fewer drug interactions, better adherence, and less patient burden over time. Response rates for switching, are based largely on open trials, which reveal a response rate of approximately 50%. These response rates are comparable to the response rates reported with augmentation or combination, again established largely by noncomparative open trials. This review article summarizes clinical considerations and available evidence regarding switching antidepressants in the treatment of major depression. Practical issues, such as when to consider switching and how to switch from one medication to another, are addressed.

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Lack of efficacy and failure to achieve remission are experienced by a substantial proportion of patients suffering from major depression, even in the context of treatment with appropriate antidepressant medication.[1] There are very few randomized controlled trials to guide treatment decisions at this common juncture, although such studies are underway. Available guidelines include the Agency for Health Care Policy and Research guideline for the treatment of depression in primary care[1] and the revised American Psychiatric Association guideline for the treatment of patients with major depressive disorder.[2] Both guidelines are evidence-based to the greatest extent possible, but recognize that the treatment decisions must be individualized, based on the clinician's judgment and patient's preference.

Options for treating antidepressant nonresponse or partial response include optimizing administration of the current medication, switching to a different antidepressant in the same class, switching to an antidepressant in a different class, adding a second antidepressant (typically of a different class), or augmenting with a nonantidepressant agent (e.g., thyroid hormone) or other therapeutic modality (e.g., psychotherapy). This article summarizes clinical considerations and available data regarding switching antidepressants in the context of adult nonpsychotic major depression. Although few controlled data to compare the efficacy of switching to a different antidepressant are available, review of the current literature indicates a response rate of about 50%.[3]

WHETHER TO SWITCH

Unless intolerable side effects are present, switching antidepressants is generally not indicated until the patient has received an adequate dose of medication for an adequate duration of time (as further discussed below). Once the patient has had an adequate trial of the current antidepressant, whether to switch, augment, or wait depends on the severity of illness, the side effects of the current medication, and the patient's willingness to take more than one medication. There are no direct comparative data to evaluate augmenting versus switching. Augmentation is perceived to have the potential for a faster response compared with discontinuing the first medication and starting a new monotherapy. For example, if a patient's depression significantly interferes with daily function such that occupational duties are compromised, augmentation should be considered if there are minimal side effects to the current antidepressant. This is particularly true if there has been a partial response (or response with residual symptoms), because the loss of even a modest degree of benefit may be demoralizing to the patient. On the other hand, a patient with milder illness, significant side effects from the current medication, a general uneasiness about taking medication,

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Table 1. Treatment Options for Nonresponse

Optimize administration of the current medication
Switch to a different antidepressant in the same class
Switch to an antidepressant in a different class
Augment with a second antidepressant (typically in a different class)
Augment with a nonantidepressant agent (eg, thyroid hormone)
Augment with a nonpharmacologic modality (eg, psychotherapy)

or minimal benefit from the initial medication may be better off if the medication is switched to a different monotherapy.

WHEN TO SWITCH?

The initial symptomatic response of the depressed patient to medication may be detected as early as the first week, but is often delayed by several weeks. An adequate trial of an antidepressant medication has been traditionally defined as treatment with therapeutic dosages of a drug for a total of 6 to 8 weeks.[2] Of note, full response and functional restoration often take longer. It is not unusual for full benefit to be delayed until 12 weeks of treatment, especially for patients with chronic depression.[4,5] For example, in a double-blind randomized trial comparing sertraline with imipramine in 635 chronically depressed outpatients, 21% of patients who achieved a therapeutic response at week 12 had not done so at week 8.[5] Except in the case of intolerable side effects, it is imperative to first ensure that the current antidepressant has been administered at an adequate dose for an adequate duration of time before either augmenting or switching. Achieving an adequate antidepressant dose is less problematic with newer nontricyclic antidepressants, but the question of an adequate duration of exposure is still problematic.

Quitkin et al.[4] and others[6] have suggested that 4 weeks may be a clinically meaningful point for reevaluation of treatment, with the important caveat that optimal dose of antidepressant medication has been used during this time. After 4 weeks of antidepressant treatment, the patient can be conceptualized as falling into 1 of 3 groups, depending on whether there has been a full response, a partial response, or no response. For the fortunate patients who achieve a full response, treatment should be continued for a minimum of 4 to 6 months, or longer if there is a history of a recurrent course or other indications for maintenance treatment. If a partial response has been achieved by week 4, a full response may be evident within an additional 2 weeks without further intervention. The risks versus benefits of a medication dose increase should be considered at this juncture. If there is no response at all (e.g., less than 25% improvement from pretreatment severity), some of the additional strategies outlined in Table 1 should be considered, with the understanding that the patient may still improve with the current treatment, but that the odds of response diminish at this point.[7,8] As such, if there is no response after 4 weeks at a therapeutic dose, particularly if troublesome adverse side effects are present, switching to a different monotherapy is a reasonable consideration. Inherent in the assessment of nonresponse is a reappraisal of the clinical situation, including previously unrecognized comorbidities and drug interactions and recent substance abuse.

DOES SWITCHING WORK?

Data from randomized controlled trials are unfortunately very limited in this area. Furthermore, many switching studies include patients who were intolerant of the first antidepressant and those with an inadequate response to an adequate medication trial. Variation in the definition of response presents another difficulty in interpreting the literature. However, in total, the clinical trial data indicate that when one antidepressant treatment fails, switching to an alternate treatment may be effective. A summary of published clinical studies of switching antidepressants in major depression is presented in Table 2. Only published prospective studies that included over 10 participants are included.

SELECTING ANOTHER ANTIDEPRESSANT

No direct comparison studies of augmenting versus switching have been published. In addition, remarkably few controlled data are available to guide the decision of switching to another medication within the same class (e.g., selective serotonin reuptake inhibitor [SSRI] to SSRI) versus a different antidepressant class (e.g., SSRI to bupropion). As with the choice of an initial antidepressant, the choice of a second agent is largely dictated by side effects, safety, patient preference, cost, drug interaction potential, and positive or negative effects of the agent on concomitant medical or psychiatric disorders. Some concomitant disorders, such as obsessive-compulsive disorder, may dictate selecting serotonergic enhancing agents. Several open studies have evaluated switching from one SSRI to another, showing a positive response rate overall.[11,15,17] However, most of these studies included SSRI-intolerant patients, as well as patients who were nonresponsive to the first SSRI. Although lacking in controlled clinical trial data, current recommendations suggest switching to an antidepressant of a different class in the event that 2 antidepressants of the same class are ineffective.[2,6]

Melancholic features include mood nonreactivity or pervasive anhedonia, early morning awakening, and diurnal mood variation with mood worse in the morning.[25] Atypical features include hypersomnia, hyperphagia, "leaden paralysis," and mood reactivity.[25] SSRIs have also been effective for atypical features in some studies.[26] Some double-blind trial data suggest that patients with melancholic features may have a preferential response to

Table 2. Summary of Clinical Studies of Switching Antidepressants in Major Depression[a]

Authors	Preswitch Treatment	Postswitch Treatment	Design	Response Rate
Stern et al, 1983[9]	TCA nonresponse or intolerance	Bupropion	Randomized controlled trial, N = 30; open, N = 33	Positive, depending on response definition and patient characteristics
McGrath et al, 1987[10]	Imipramine or phenelzine	Imipramine or phenelzine	Randomized crossover, N = 101	Phenelzine, 65%; imipramine, 29%
Joffe et al, 1996[11]	Fluoxetine	Sertraline	Open, N = 55	52%
Nolen et al, 1988[12]	TCA	Fluvoxamine or oxaprotiline	Double-blind partial crossover of nonresponders, N = 71	13% combined (oxaprotiline, 27%; fluvoxamine, 0%; subsequent crossover, oxaprotiline 39%; fluvoxamine, 10%)
Beasley et al, 1990[13]	TCA	Fluoxetine	Open, N = 132	62% vs 51%, depending on the definition of refractoriness
Thase et al, 1992[14]	Imipramine	MAOI	Open, N = 42	58%, more among subjects with atypical features
Brown and Harrison, 1992[15]	Fluoxetine intolerance	Sertraline	Open, N = 100	76%
Nierenberg et al, 1994[16]	3 prior adequate trials	Venlafaxine	Open, N = 84	33%
Thase et al, 1997[17]	Sertraline nonresponse or intolerance	Fluoxetine	Open, N = 106	63%
Thase et al,[18] in press	Sertraline or imipramine	Sertraline or imipramine	Randomized crossover, N = 168	Over 50% in both groups

[a]Abbreviations: MAOI = monoamine oxidase inhibitor, TCA = tricyclic antidepressant.

tricyclic antidepressants (TCAs).[19–21] Patients with atypical features have a higher response rate to monoamine oxidase inhibitors (MAOIs) compared with TCAs based on randomized controlled clinical trials.[14,22–24] Because both TCAs and MAOIs have a greater side effect burden and potential toxicity than most of the newer agents, most clinicians do not use these agents for first-line treatment. However, it may be reasonable to consider TCAs or MAOIs for patients with either melancholic or atypical symptom features if other medications have not been effective.

HOW TO SWITCH

Often clinicians will choose to discontinue the first medication before starting the second one. However, in most instances there is not a critical need for a medication-free period, if neither medication is an MAOI. In many instances, it is possible to start the new drug while tapering the first. This overlapping of medications is sometimes helpful to minimize patient discomfort, but must be weighed against the risk of increased side effects and drug interactions. For example, some patients report increased side effects and anxiety when switching from fluoxetine to nefazodone. This reaction is most likely because fluoxetine and its active metabolite (norfluoxetine) inhibit cytochrome P450 2D6 (CYP2D6), which may lead to accumulation of *m*-chlorophenylpiperazine (*m*-CPP). *m*-CPP is a metabolite of nefazodone that is reliant on the 2D6 enzyme for excretion. This interaction exemplifies some of the considerations when switching antidepressants, namely, half-life and drug interactions. A similar reaction is possible with other antidepressants that inhibit CYP2D6, and the duration of risk is proportional to the half-life of the inhibitor (e.g., shorter for paroxetine than for fluoxetine due to differences in half-life). A drug is eliminated in the amount of time equal to 5 times the half-life of the drug, including any active metabolites.

SWITCHING SPECIFIC ANTIDEPRESSANTS

MAOI to and From Another Antidepressant

Particular care must be taken when switching patients from an MAOI to another antidepressant. For patients who have completed an MAOI trial without therapeutic response, other antidepressants should not be started until 14 days after the original MAOI has been discontinued. Equal care is required when switching from one MAOI to another. A time period equal to 5 times the half-life of the drug, including active metabolites, is required between stopping other antidepressants and starting an MAOI. However, MAOIs may be safely begun, with the appropriate precautions, while a patient continues treatment with TCAs,[27] although the evidence for this combination has not been established in randomized controlled trials.

SSRI to SSRI

SSRIs currently available in the United States are citalopram, fluoxetine, fluvoxamine, sertraline, and parox-

etine. Switching from one SSRI to another can be accomplished by a direct swap of one drug for the next. Although the abrupt discontinuation of SSRIs, particularly those with a short half-life (e.g., paroxetine), may be associated with discontinuation effects,[28] this effect is not seen if another medication is substituted that also inhibits the serotonin reuptake pump. Although the sophisticated clinician will realize that both agents will be present for a time period equal to 5 times the half-life of the first medication, this is not usually a problem in practice. Similarly, higher levels of either medication may occur if one or both medications inhibit cytochrome enzymes (e.g., paroxetine or fluoxetine). This may lead to transient side effects, but is not usually a safety issue. In most cases, a direct swap is better tolerated than washout of the first agent. Equivalent doses of SSRIs have not been clearly established. When choosing the dose of the new SSRI, consider if the original SSRI was being dosed at the low, middle, or high end of the known therapeutic range and use a similar range for the new antidepressant. A third option is a cross-taper. Cross-tapering refers to the practice of gradually increasing the new medication while simultaneously decreasing the dose of the original medication. While cross-tapering may be useful when medications with different receptor effects are used (e.g., SSRI to bupropion or mirtazapine) there is no utility for this strategy when both medications are SSRIs.

SSRI To/From Venlafaxine

Because venlafaxine inhibits the serotonin reuptake pump, a direct switch from an SSRI to venlafaxine (or vice versa) will not result in discontinuation-emergent effects. However, care should be exercised when one of the medications (e.g., paroxetine or fluoxetine) inhibits CYP2D6, because resultant inhibition of venlafaxine metabolism has been associated with cardiovascular[29] and serotonergic side effects.[30] As with the SSRI-to-SSRI switch, cross-tapering is generally not beneficial when switching between SSRIs and venlafaxine. Similarly, the discomfort to patients of tapering and washing out the first medication must be considered. In many cases, a direct switch is advisable.

SSRI To/From Bupropion

Switching from an SSRI to bupropion is often chosen when the patient has experienced sexual dysfunction in addition to a less-than-optimal antidepressant response on treatment with an SSRI and there are no comorbid anxiety disorders that would dictate a different medication. On the other hand, switching from bupropion to an SSRI is often undertaken in patients with comorbid anxiety that has not responded to bupropion. Because these medications have different receptor effects, a direct switch is not advisable. For example, switching from paroxetine to bupropion without tapering may lead to discontinuation symptoms, because bupropion affects the norepinephrine and dopamine reuptake pumps, but not the serotonin reuptake pump. Therefore, it is best to gradually taper the SSRI, which can be done while a low dose of bupropion is started (cross-tapering).

SSRI To/From Nefazodone

An SSRI/nefazodone switch may be complicated by drug interactions. In addition, there are reports of nonlethal serotonin syndrome when SSRIs and nefazodone are administered concurrently.[31,32] Because these medications are mechanistically different, a direct swap of one drug for the other may not abate discontinuation symptoms from the first drug. For these reasons, it may be worthwhile to taper the first drug and allow a brief washout period before beginning the second drug when switching from SSRIs to nefazodone (or vice versa).

SSRI To/From Mirtazapine

Because these medications are mechanistically distinct and there is no concern for serious drug interactions when they are administered together, a cross-taper is often a reasonable approach to this switch.

SSRI To/From TCA

The primary concerns when switching from an SSRI to a TCA (or vice versa) are avoiding drug interactions that risk TCA toxicity and avoiding discontinuation effects when stopping the first medication. Because fluvoxamine inhibits CYP1A2 and CYP3A3/4, concurrent administration with amitriptyline or imipramine will lead to decreased clearance of the TCA. Because the 2D6 enzyme is a final common metabolic pathway for TCAs, paroxetine and fluoxetine may lead to increased TCA levels, which may result in increased side effects or toxicity. To anticipate the potential for this reaction, a lower dosage of the TCA should be used when administered concurrently with or proximate to an SSRI that may inhibit TCA metabolism. In addition, abrupt discontinuation of TCAs may lead to cholinergic rebound, which is not prevented by switching to an SSRI. As such, this is an instance in which cross-tapering may be effective.

Venlafaxine To/From Bupropion, Nefazodone, or Mirtazapine

Because these medications are all mechanistically distinct and venlafaxine is not a significant inhibitor of CYP450 enzymes, a cross-taper is often a reasonable approach to switching to or from venlafaxine and bupropion, nefazodone, or mirtazapine.

Bupropion To/From Nefazodone or Mirtazapine

Once again, these medications are all mechanistically distinct. A cross-taper is often a reasonable approach to switching between these agents.

WHAT NEXT?

The Texas Medication Algorithm Project consensus panel recommends electroconvulsive therapy (ECT) after 3 ineffective treatments for major depressive disorder without psychotic features.[6] Although ECT is clearly an effective treatment, many patients prefer to explore other alternatives. Augmentation strategies (discussed separately in this supplement[33]) are a viable option for many patients. Vagus nerve stimulation, although experimental, has shown promising preliminary results.[34]

CONCLUSIONS

Multiple options are available for patients who do not adequately respond to an initial course of antidepressants. Switching to a different antidepressant is one such strategy. Although the focus of this article is pharmacotherapy, psychotherapy is equally important for many patients. Although controlled clinical trial data are limited to date, open studies and retrospective analysis suggest an average efficacy rate of about 50%. It is also important to note that this review does not address the unique needs of patients with subtypes of depression that require other specific interventions. For example, patients with psychotic depression require both an antidepressant and an antipsychotic[35] or ECT,[36] and patients with bipolar depression require the use of a mood stabilizer. Another highly important clinical issue that is not well addressed in the switching studies to date is the impact of residual symptoms. Patients with residual subthreshold depressive symptoms relapse to depressive episodes more than 5 times faster than patients with asymptomatic recovery[37] and also tend to have a more severe and chronic future course of illness. Accordingly, the clinical goal is to achieve not just response (improvement), but remission (wellness) and optimal functioning.[38]

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author has determined that, to the best of her knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

REFERENCES

1. Clinical Practice Guideline Number 5: Depression in Primary Care, vol 2. Treatment of Major Depression. Rockville, Md: US Dept Health Human Services, Agency for Health Care Policy and Research; 1993. AHCPR publication 93-0551
2. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Major Depressive Disorder [Revision]. Am J Psychiatry 2000;157(suppl 4):1–45
3. Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press; 1995:1081–1097
4. Quitkin FM, McGrath PJ, Stewart JW, et al. Chronological milestones to guide drug change: when should clinicians switch antidepressants? Arch Gen Psychiatry 1996;53:785–792
5. Keller MB, Gelenberg AJ, Hirschfeld RMA, et al. The treatment of chronic depression, pt 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59:598–607
6. Crismon ML, Trivedi M, Pigott TA, et al. The Texas Medication Algorithm Project: report of the Texas Consensus Conference Panel on Medication Treatment of Major Depressive Disorder. J Clin Psychiatry 1999;60: 142–156
7. Nierenberg AA, McLean NE, Alpert JE, et al. Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152: 1500–1503
8. Trivedi MH, Kleiber BA. Algorithm for the treatment of chronic depression. J Clin Psychiatry 2001;62(suppl 6):22–29
9. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. J Clin Psychiatry 1983;44(5, sec 2):148–152
10. McGrath PJ, Stewart JW, Harrison W, et al. Treatment of tricyclic refractory depression with a monoamine oxidase inhibitor antidepressant. Psychopharmacol Bull 1987;23:169–172
11. Joffe RT, Levitt AJ, Sokolov STH, et al. Response to an open trial of a second SSRI in major depression. J Clin Psychiatry 1996;57:114–115
12. Nolen WA, van de Putte JJ, Dijken WA, et al. Treatment strategy in depression, I. Non-tricyclic and selective reuptake inhibitors in resistant depression: a double-blind partial crossover study on the effects of oxaprotiline and fluvoxamine. Acta Psychiatr Scand 1988;78:668–675
13. Beasley CM Jr, Sayler ME, Cunningham GE, et al. Fluoxetine in tricyclic refractory major depressive disorder. J Affect Disord 1990;20:193–200
14. Thase ME, Frank E, Mallinger AG, et al. Treatment of imipramine-resistant recurrent depression, 3: efficacy of monoamine oxidase inhibitors. J Clin Psychiatry 1992;53:5–11
15. Brown WA, Harrison W. Are patients who are intolerant to one SSRI intolerant to another? Psychopharmacol Bull 1992;28:253–256
16. Nierenberg AA, Feighner JP, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol 1994;14:419–423
17. Thase ME, Blomgren SL, Birkett MA, et al. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. J Clin Psychiatry 1997;58:16–21
18. Thase ME, Rush AJ, Howland RH, et al. Double-blind cross-over study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry. In press
19. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Psychopharmacology (Berl) 1986;90:131–138
20. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
21. Perry PJ. Pharmacotherapy for major depression with melancholic features: relative efficacy of tricyclic versus selective serotonin reuptake inhibitor antidepressants. J Affect Disord 1996;39:1–6
22. Liebowitz MR, Quitkin FM, Stewart JW, et al. Antidepressant specificity in atypical depression. Arch Gen Psychiatry 1988;45:129–137
23. Quitkin FM, Rifkin A, Klein DF. Monoamine oxidase inhibitors: a review of antidepressant effectiveness. Arch Gen Psychiatry 1979;36:749–760
24. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995;12:185–219
25. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
26. Pande AC, Birkett M, Fechner-Bates S, et al. Fluoxetine versus phenelzine in atypical depression. Biol Psychiatry 1996;40:1017–1020
27. Kahn D, Silver JM, Opler LA. The safety of switching rapidly from tricyclic antidepressants to monoamine oxidase inhibitors. J Clin Psychopharmacol 1989;9:198–202
28. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. Biol Psychiatry 1998;44:77–87
29. Lessard E, Yessine MA, Hamelin BA, et al. Influence of CYP2D6 activity on the disposition and cardiovascular toxicity of the antidepressant agent venlafaxine in humans. Pharmacogenetics 1999;9:435–443
30. Bhatara VS, Magnus RD, Paul KL, et al. Serotonin syndrome induced by

venlafaxine and fluoxetine: a case study in polypharmacy and potential pharmacodynamic and pharmacokinetic mechanisms. Ann Pharmacother 1998;32:432–436
31. John L, Perreault MM, Tao T, et al. Serotonin syndrome associated with nefazodone and paroxetine. Ann Emerg Med 1997;29:287–289
32. Smith DL, Wenegrat BG. A case report of serotonin syndrome associated with combined nefazodone and fluoxetine [letter]. J Clin Psychiatry 2000; 61:146
33. Fava M. Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 18):4–11
34. Rush AJ, George MS, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depressions: a multicenter study. Biol Psychiatry 2000 15;47(4):276–286
35. Spiker DG, Weiss JC, Dealy RS, et al. The pharmacological treatment of delusional depression. Am J Psychiatry 1985;142:430–436
36. American Psychiatric Association. The Practice of Electroconvulsive Therapy: Recommendations for Treatment, Training, and Privileging: A Task Force Report of the American Psychiatric Association. Washington, DC: American Psychiatric Association; 1990
37. Judd LL, Akiskal HS, Maser JD, et al. Major depressive disorder: a prospective study of residual subthreshold depressive symptoms as predictor of rapid relapse. J Affect Disord 1998;10:97–108
38. Rush AJ, Trivedi MH. Treating depression to remission. Psychiatr Ann 1995;25:704–705, 709