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Considerations And Factors For Switching And Augmenting Medications For Major Depressive Disorder

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Objectives

- To discuss treatment challenges and guidelines for treating major depressive disorder (MDD)
- To consider recommendations from the literature regarding making a treatment change for patients with partial or non-response to current treatment
- To understand considerations from the literature regarding switch vs. augmentation as a treatment strategy for patients with partial or non-response
- To explore physician determinants of use of antipsychotic treatment augmentation for patients with MDD

MDD, major depressive disorder.

Treatment Challenges In Major Depressive Disorder (MDD)

- In 2015, an estimated 16.1 million adults 18 years or older in the United States (US) had at least 1 major depressive episode in the past year. This represented 6.7% of all US adults[1]
- Residual symptoms have been associated with significant psychosocial disability and faster relapse compared with asymptomatic remission[2]
- Patients with residual symptoms are also at significantly higher risk of relapse than those without and may have social and/or occupational impairments[2]
  - The presence of mild residual symptoms has been found to be an even stronger predictor of subsequent relapse than prior history of MDD
- In 1 study, the MDD treatment response rate dropped and risk for relapse increased as the number of treatments increased[3]
- In a study of US patients treated for a depressive disorder (N = 56,521):
  - 8.6% (n = 4844) switched antidepressants during the first 90 days of therapy[4]:
    - 2.4% (n = 1333) added a second antidepressant as an adjunctive agent
- In a survey* of patients (n=597) with MDD with inadequate response to antidepressant treatment, 39% reported feeling frustrated with their medication. This frustration led patients to (n=200):[5†]
  - Want to quit taking medication all together (34%)
  - Question the abilities of their health care provider (22%)
  - Not take their medication on a regular basis (16%)

*Otsuka-sponsored study. †Not a complete list; other outcomes identified in the original study.

1. NIMH/NIH.gov Health Statistics website. http://www.nimh.nih.gov/health/statistics/prevalence/major-depression-among-adults.shtml. Accessed May, 2017.
2. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
3. Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905–1917.
4. Marcus S, et al. *Psychiatr Serv.* 2009;60:617–623.
5. Mago R, et al. Presented at the *29th Annual U.S. Psychiatric & Mental Health Congress*, held October 21-24, 2016, in San Antonio, Texas

Guideline Recommendations For Treating Adults With MDD

2 sets of treatment guidelines emerged in 2010*:

- APA Practice Guidelines for MDD Treatment[1]
  - Summarizes specific approaches to treatment of patients with MDD and outlines recommendations for formulation and implementation of a treatment plan
    - Covers psychiatric management, management of patients in the acute, continuation, and maintenance phases, treatment discontinuation, and provides an overview of clinical factors influencing treatment
  - Some key recommendations include:
    - Evaluating functional impairment and quality of life, coordinating care with other clinicians, and integrating measurements into psychiatric management (rating scales)
    - Antidepressants are recommended as an initial treatment choice for patients with mild to moderate MDD and for those with severe MDD unless ECT is planned
    - ECT is recommended if patients with severe MDD are not responsive to psychotherapy and/or pharmacologic interventions
    - Depression-focused psychotherapy alone is recommended for as an initial treatment choice for patients with mild to moderate MDD

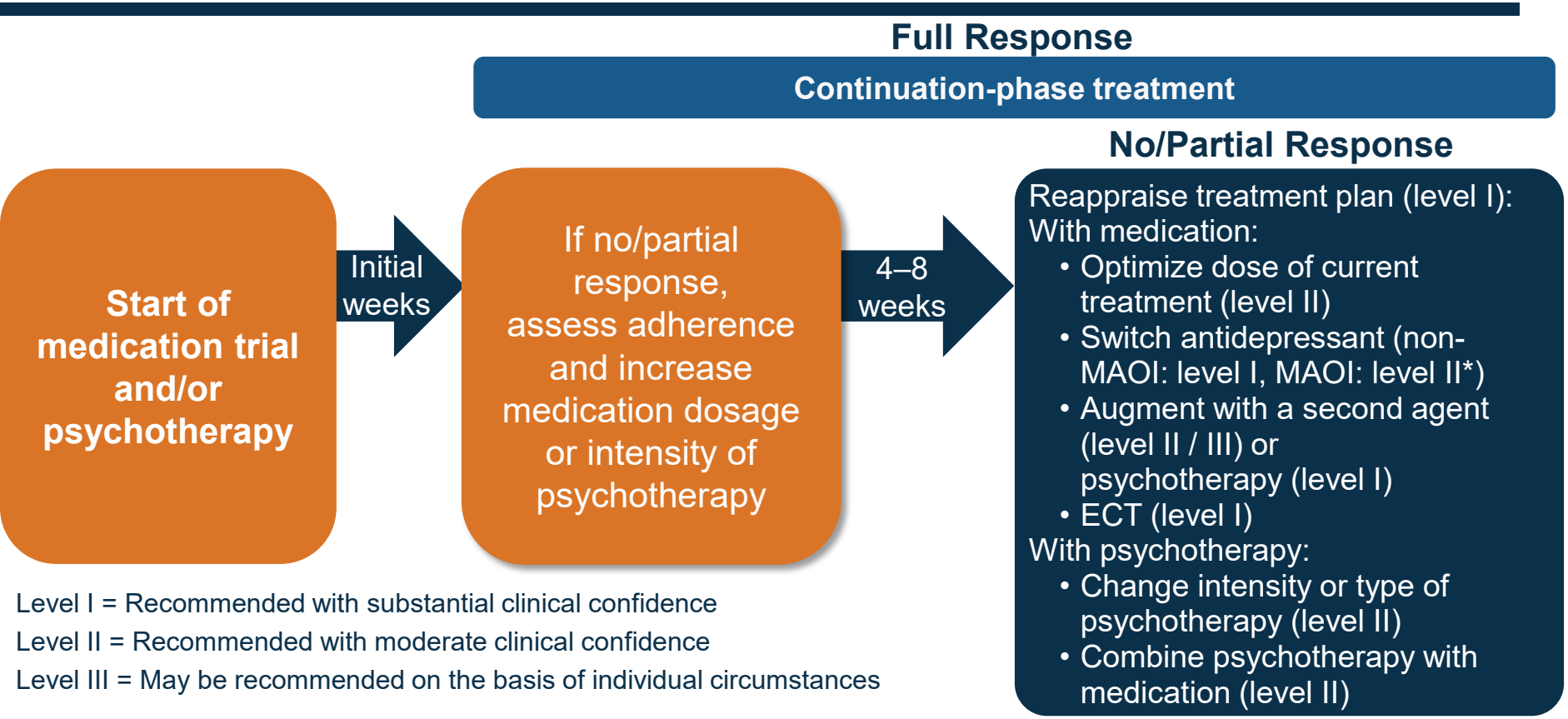
- An International Consensus Guideline developed by a panel of psychiatric experts outlined a universal treatment algorithm for MDD[2]
  - Provides a general consensus to merge evidence and standardize clinical practice
    - Across treatment guidelines from the US, Europe, Japan, China, and the Middle East
  - Outlines basic strategies for detecting, diagnosing, and treating acute MDD
  - Some key recommendations:
    - All patients should be screened for depression
    - Appropriate tools and clinical judgment should be utilized for accurate diagnosis
    - Patients should be treated with an antidepressant and their treatment response and side effects assessed regularly using monitoring tools (measurement-based care) to ensure that patients reach and maintain remission

***These parameters of practice should be considered guidelines only and not standard of medical care.**

APA, American Psychiatric Association; ECT, electroconvulsive therapy; MDD, major depressive disorder; US, United States.

1. American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
2. Nutt DJ, et al. *J Clin Psychiatry*. 2010;71[suppl E1]:e08.

APA Guidelines For The Acute-Phase Treatment Of MDD



Level I = Recommended with substantial clinical confidence

Level II = Recommended with moderate clinical confidence

Level III = May be recommended on the basis of individual circumstances

These parameters of practice should be considered guidelines only and not standard of medical care.

*Switch to MAOI as an option only if patients can adhere to dietary and medication restrictions, and after allowing enough time between medications to avoid any adverse interactions.

APA, American Psychiatric Association; ECT, electroconvulsive therapy; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder.

Adapted from American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

APA Guidelines: Augmentation Recommendations For No/Partial Response To Antidepressant Therapy

Augmentation Options*	Level of Clinical Confidence (I–III)‡
Psychotherapy	I
Second antidepressant therapy†	II
Atypical antipsychotic treatment	
Thyroid hormone	
Mood stabilizer	
Anticonvulsant	III
Psychostimulant	
Omega-3 fatty acid	
Folic acid	
Anxiolytic or sedative/hypnotic	

*Classes of medication have been used in this table to replace some of the specific drug names.
†Includes non-MAOI and MAOI antidepressants.
‡Level I, recommended with substantial clinical confidence; level II, recommended with moderate clinical confidence; level III, may be recommended on the basis of individual circumstances.
APA, American Psychiatric Association.

Adapted from American Psychiatric Association. *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

International Consensus Statement On Optimizing Antidepressant Therapy

- Begin pharmacotherapy with an SSRI, SNRI, or NDRI
- After reaching a minimally effective dose, wait approximately 2 to 4 weeks to assess symptomatic improvement and tolerability before deciding how to optimize therapy:

Increase the Dose: In cases of inadequate improvement but acceptable tolerability

Maintain the Current Dose: In cases of adequate improvement and acceptable tolerability

Decrease the Dose: In cases of adequate improvement but poor tolerability

Switch the Patient to a Different Agent: In cases of inadequate improvement and poor tolerability

- Assessment of symptomatic improvement and tolerability should occur every 2 weeks and at each assessment. Reasonable treatment options for partial or lack of efficacy include:

Modifying the antidepressant dose

Switching to a different antidepressant

Switching to augmentation/ combination strategies

- Augmentation/combination strategies include, but are not limited to: mood stabilizers, atypical antipsychotics, thyroid hormone, NaSSA, or NDRI*

*Not all products in the therapeutic categories listed are indicated for adjunctive treatment in adult patients with MDD with an inadequate response to antidepressant therapy. Classes of medication have been used to replace some of the specific drug names. Please see the International Consensus Statement for further information on specific drug recommendation options for ADT augmentation.

ADT, antidepressant therapy; NaSSA, noradrenergic and specific serotonergic antidepressant; MDD, Major Depressive Disorder; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor .

Nutt DJ et al. *J Clin Psychiatry*. 2010;71(suppl E1):e08.

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Implementing A Treatment Change: Strategies For Partial Or Non-Response

MDD Treatment Response Strategy

- Patients with MDD often fail to respond to first-line treatment[1]
- In the comprehensive STAR*D trial*, as many as two-thirds of patients with MDD failed to experience remission following initial treatment with a first-line antidepressant[2]
- In a study of outcomes of STAR*D patients requiring one or more treatment steps:[3]
  - Switching treatment strategies resulted in adequate symptom relief in approximately 1 in 4 patients switched to a different antidepressant
  - Adjunctive treatment strategies, when initiated after inadequate response to antidepressant therapy, resulted in adequate symptom relief in approximately 1 in 3 patients†

*Antipsychotics were not included in the STAR*D trial. †This was not a randomized study and the patient population was different in each group. Therefore, direct comparisons between switching and adjunctive treatment strategies cannot be made.
MDD, major depressive disorder; STAR*D, Sequence Treatment Alternatives to Relieve Depression.

1. McIntyre RS, et al. *Adv Ther.* 2015;32:429–444.
2. Trivedi MH, et al. *Am J Psychiatry*. 2006;163:28-40.
3. Rush AJ et al. *N Engl J Med.* 2006;354:1231-1242.

Considerations in Switching From A Failed Previous Treatment

Recommendations from the literature

- Prior to initiating treatment, differentiate between a depressive relapse during antidepressant use and nonresponse to an antidepressant
- Obtain a detailed history to ascertain whether the patient achieved near or full remission during the most recent depressive episode
- Rule out nonadherence
- Establish adequacy of treatment
- Conduct a diagnostic reassessment
- Confirm or change diagnosis

Papakostas G. *J Clin Psychiatry*. 2009;70[suppl 6]:16–25.

Steps In Deciding To Make A Treatment Change

Recommendations from the literature

- Choose evidence-based treatment strategies
- Evaluate the patient:
  - Take a detailed history
  - Confirm diagnosis
  - Confirm adequacy of and adherence to first-line treatment
  - Assess for comorbid and psychiatric diagnoses
  - Differentiate between nonresponse to treatment and depressive relapse
- Consider the tolerability of first-line treatment and the possible loss of benefit of first-line agent when considering treatment switching, combination, or augmentation strategies

Papakostas G. *J Clin Psychiatry*. 2009;70[suppl 6]:16–25.

Switch Versus Augmentation As An Antidepressant Treatment Strategy

Considerations From the Literature

Advantages of Switching*

- Lower risk of drug interactions
- Potentially, better patient compliance (fewer medications)
- Less costly in some cases
- Favorable for patients who experience intolerable side effects and minimal symptom improvement on first-line therapy

Advantages of Augmentation†

- Minimize the loss of any therapeutic benefit from the first-line agent
- Avoid withdrawal symptoms that may occur upon switching
- Target (offset) side effects of the first-line therapy

*Advantages over augmentation or combination therapy. †Advantages of augmentation and combination strategies versus switching.

Papakostas G. *J Clin Psychiatry*. 2009;70[suppl 6]:16–25.

Considerations From The Literature In Forming An Augmentation Strategy For Inadequate Responders

- Avoid contraindications
- Target a cumbersome symptom → rapid relief before full antidepressant response is achieved
- Consider comorbidities → minimize number of medications prescribed
- Consider compliance (i.e., cost, side effects, dosing regimen)
- Consider the weight of the clinical evidence for the effectiveness of a given strategy

Blier P. *Int J Neuropsychopharm*. 2014;17:997–1008.

Augmentation Strategies For MDD

- Based on the cumulative evidence in the last decade, augmentation strategies are recommended in most guidelines for partial or non responders in clinical practice. Such strategies include:[1]
  - SGA augmentation
  - Switching to different antidepressants
  - A combination of different antidepressant strategies
- Among second-treatment steps, the augmentation strategy has proven its usefulness for:[1]
  - Enhancing antidepressant effect
  - Showing increased remission rates and early treatment effects on core depressive symptoms and comorbid symptoms without losing previous antidepressant response
  - Minimizing antidepressant-mediated side effects (e.g., sexual dysfunction)
- Although classical augmentation agents have been commonly used for patients with inadequate response to antidepressant first-line therapy, their use is supported by limited data and none have been officially approved by the US FDA[1]
- SGAs have demonstrated efficacy as an augmentation agent for MDD patients through a number of small-scale, open-label studies or randomized, placebo-controlled clinical trials[1]
- Atypical antipsychotics are the most studied class of augmenting agents to SSRIs and SNRIs for depression[2]

FDA, Food and Drug Administration; MDD, Major Depressive Disorder; SGA, second-generation antipsychotic; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; US, United States.

1. Han C, et al. *Expert Rev Neurother*. 2013;13(7):851-70.
2. Ionescu DF, et al. *Alpert Dialogues Clin Neurosci*. 2015; 17(2): 111–126.

Potential Net Effects Relating To Neurotransmission And Other Actions Of Second-Generation Antipsychotics

Enhancement of dopaminergic neurotransmission
- 5-HT_{1A} receptor agonism
- 5-HT_{2A} receptor antagonism
- 5-HT_{2C} receptor antagonism
- α-2 receptor antagonism
- 5-HT_6 receptor antagonism
- Serotonin transporter inhibition

Enhancement of serotonergic neurotransmission
- 5-HT_7 receptor antagonism
- α-2 receptor antagonism
- Serotonin transporter inhibition

Enhancement of noradrenalin neurotransmission
- 5-HT_{2C} receptor antagonism
- α-2 receptor antagonism
- 5-HT_6 receptor antagonism
- Norepinephrine transporter inhibition

Miscellaneous effects
- Neuroprotection (eg, glutamate excitotoxicity and neuromodulation)
- Hormonal modulation (eg, corticotropin-releasing factor, cortisol and adrenocorticotropic hormone)
- Sleep alteration

α, alpha; 5-HT, serotonin.

Han C, et al. *Expert Rev Neurother*. 2013;13(7):851-70.

Real-World Determinants Of Adjunctive Antipsychotic Prescribing For Patients With MDD

- In a case review study* conducted to determine why patients with MDD and an inadequate response to antidepressant treatment were prescribed an adjunctive antipsychotic, psychiatrists and primary care physicians (n = 411) were surveyed

In this study, the most common reasons providers chose to prescribe adjunctive antipsychotics were:

- To achieve better efficacy/symptom control
- Familiarity with product
- The patient's level of functioning
  - Adjunctive antipsychotics were prescribed to those with greater functional impairment
- A better tolerability profile
- The patient's history of MDD
  - Prescription of an adjunctive antipsychotic was more common among patients that had
    - More previous major depressive episodes
    - A higher CGI-S score at initiation and at current consultations
    - More previous treatment changes
    - Longer duration of the current depressive episode

*Otsuka-funded study; surveyed psychiatrists and primary care physicians (n=411) based in the United States and Europe.
CGI-S, Clinical Global Impression Scale-Severity; MDD, major depressive disorder.

McIntyre RS, et al. *Adv Ther*. 2015;32:429–444.

Real-World Determinants Of Adjunctive Antipsychotic Prescribing For Patients With MDD (cont)

- In a case review study* conducted to determine why patients with MDD and an inadequate response to antidepressant treatment were prescribed an adjunctive antipsychotic, psychiatrists and primary care physicians (n = 411) were surveyed

In this study, the most common reasons providers chose NOT to prescribe adjunctive antipsychotics were:

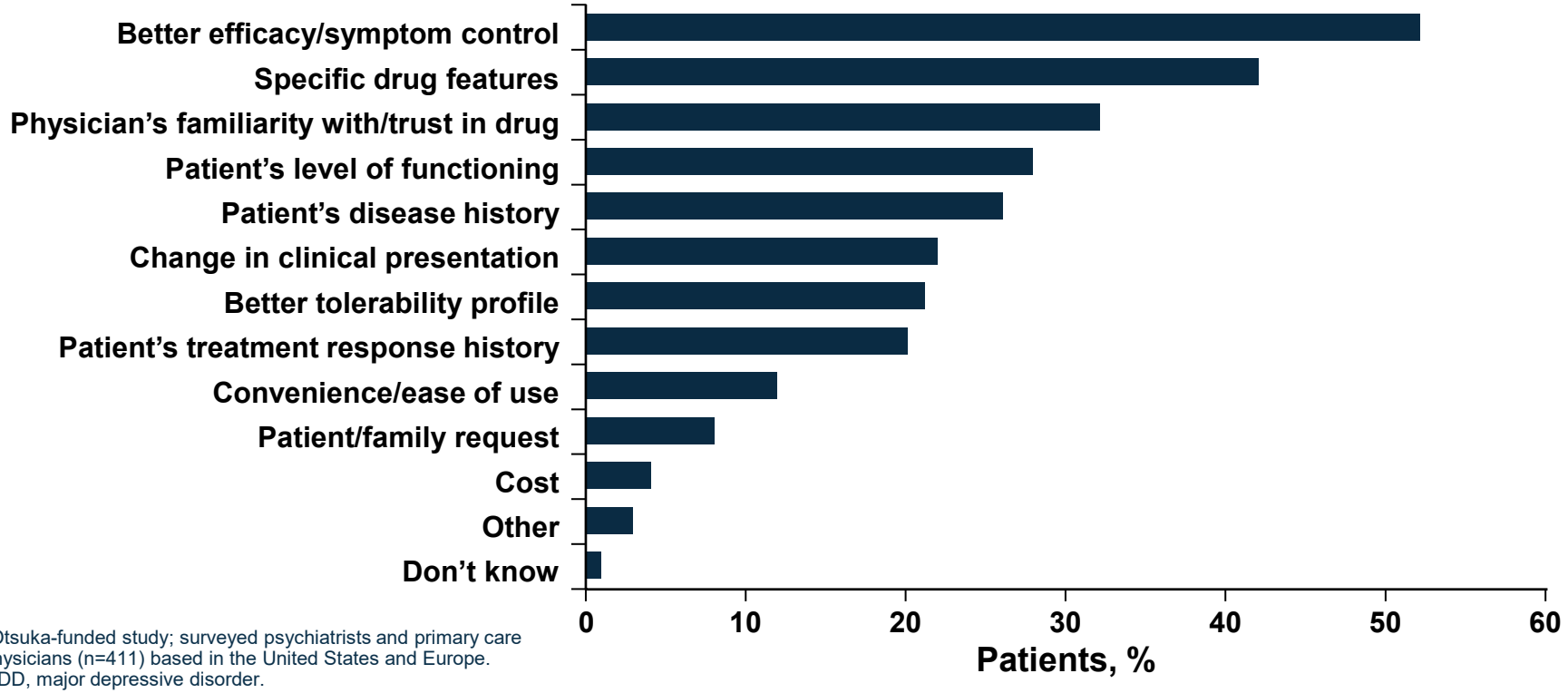
- A preference to wait and see if symptoms improve
- Tolerability or safety concerns
- A preference to reserve antipsychotics for MDD patients with specific symptoms. The most frequently cited symptoms were:
  - Psychotic symptoms (66.4%)
  - Psychomotor agitation (35.3%)
  - Hostility (32.9%)
  - Irritability (28.8%)
  - Impulsivity (28.1%)
  - Bursts of anger (27.1%)

*Otsuka-funded study; surveyed psychiatrists and primary care physicians (n=411) based in the United States and Europe.
MDD, major depressive disorder.

McIntyre RS, et al. *Adv Ther*. 2015;32:429–444.

Physicians' Reasons For Deciding To Prescribe An Adjunctive Antipsychotic Medication

- In a case review study* conducted to determine why patients with MDD and an inadequate response to antidepressant treatment were prescribed an adjunctive antipsychotic, psychiatrists and primary care physicians (n = 411) were surveyed
- Practitioners' reasons for prescribing adjunctive antipsychotic medication were:

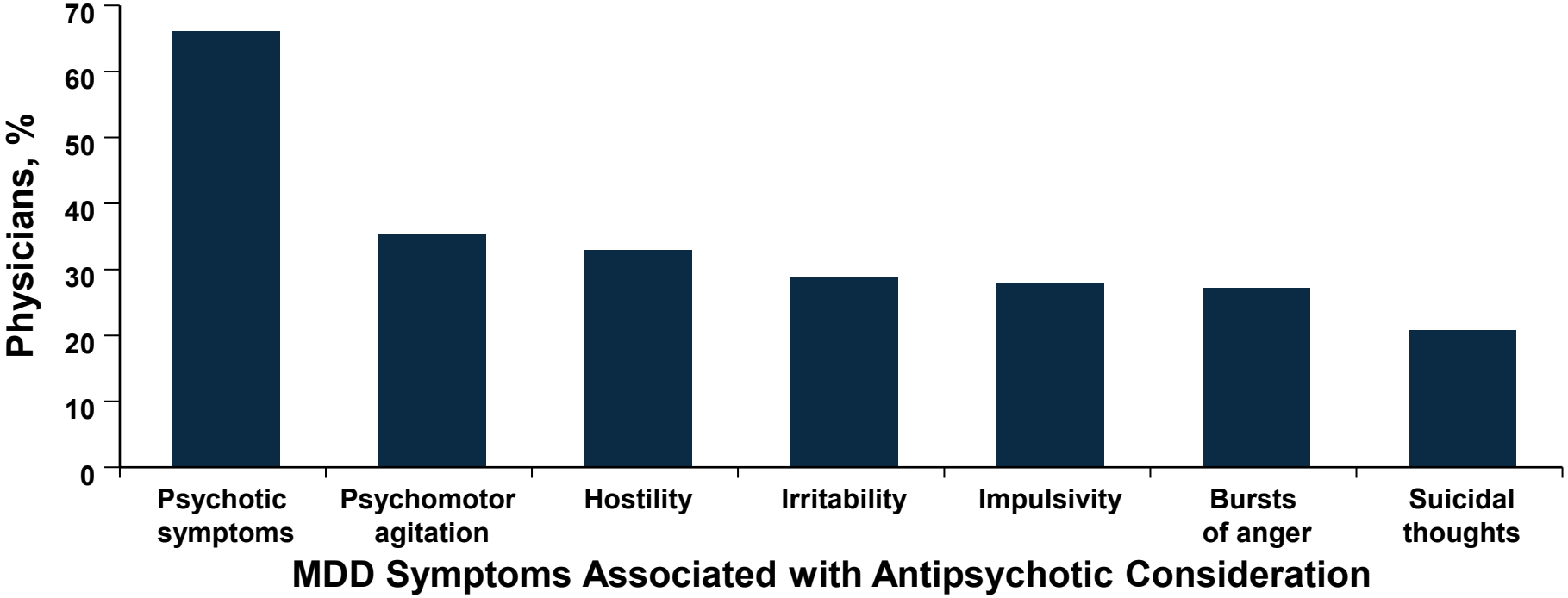


*Otsuka-funded study; surveyed psychiatrists and primary care physicians (n=411) based in the United States and Europe.
MDD, major depressive disorder.

McIntyre RS, et al. *Adv Ther*. 2015;32:429–444.

Symptoms For Which Physicians Preferred To Reserve Antipsychotic Treatment

- In a case review study* conducted to determine why patients with MDD and an inadequate response to antidepressant treatment were prescribed an adjunctive antipsychotic, psychiatrists and primary care physicians (n = 411) were surveyed
- In this study, health care providers (n = 295) expressed a preference to reserve antipsychotics for patients with specific symptoms. The most frequently identified symptoms were:



*Otsuka-funded study; surveyed psychiatrists and primary care physicians (n=411) based in the United States and Europe.
MDD, major depressive disorder.

McIntyre RS, et al. *Adv Ther*. 2015;32:429–444.

Summary

- There are several considerations and recommendations from the literature regarding making treatment changes for patients with partial or non-response to current treatment[1]
- Several factors should be considered when choosing between augmentation and switching strategies[2]:
  - Tolerability of the first-line treatment
  - The potential loss of partial benefit from the first-line antidepressant
  - The risk of withdrawal symptoms when switching agents
  - The risk of drug interactions
  - Compliance problem
- Augmentation strategies should[3]:
  - Avoid contraindications
  - Consider potential symptom relief and comorbidities
  - Consider clinical evidence
- There are a variety of determinants used by physicians when considering prescription of adjunctive antipsychotics for patients with MDD[4]
  - Atypical antipsychotics are the most studied class of augmenting agents to SSRIs and SNRIs for depression[5]

MDD, Major Depressive Disorder; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

1. Han C, et al. *Expert Rev Neurother*. 2013;13(7):851-70.
2. Papakostas G. *J Clin Psychiatry*. 2009;70[suppl 6]:16–25.
3. Blier P. *Int J Neuropsychopharm*. 2014;17:997–1008.
4. McIntyre RS, et al. *Adv Ther*. 2015;32:429–444.
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