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Supplementary Material

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Authors: Joseph F. Goldberg, MD, MS; Gin S. Malhi, MD; Manish K. Jha, MD; A. John Rush, MD; Rajnish Mago, MD; Anita H. Clayton, MD; Leslie Citrome, MD, MPH; Holly A. Swartz, MD; Marlene P. Freeman, MD; Michael Berk, PhD, MBBCh; Siegfried Kasper, MD; Roger S. McIntyre, MD; Sheldon H. Preskorn, MD; Andrea Fagiolini, MD; Dan V. Iosifescu, MD; M. Lynn Crismon, PharmD, Lawrence J. Cohen, PharmD; S. Nassir Ghaemi, MD; John S. Markowitz, PharmD; Taeho Greg Rhee, PhD; Eduard Vieta, MD, PhD; Henry A. Nasrallah, MD; Christoph U. Correll, MD; Chittaranjan Andrade, MD; Michael E. Thase, MD; Mauricio Tohen, MD, DrPH, MBA; Matthew Macaluso, DO; Richard C. Shelton, MD Charles B. Nemeroff, MD, PhD; Carlos A. Zarate, Jr, MD; Michael J. Gitlin, MD; Lars V. Kessing, MD; Beny Lafer, MD; Allan H. Young, MPhil, MBChB; Stephen M. Stahl, MD, PhD; Ralph Kupka, MD; Konstantinos N. Fountoulakis, MD, PhD; Robert M. Post, MD; David L. Dunner, MD; Adele C. Viguera, MD; Deanna L. Kelly, PharmD; Lakshmi N. Yatham, MD; Joshua D. Rosenblat, MD, MSc; Scott T. Aaronson, MD; Mark A. Frye, MD; John R. Geddes, MD; Guy M. Goodwin, MD; Suzanne C. Harris, PharmD; Philip Gorwood, MD; David S. Baldwin, MD; Andrew A. Nierenberg, MD; John M. Kane, MD; Michael J. Ostacher, MD, MPH, MMSc; Martin Alda, MD; Anthony J. Rothschild, MD Alessandro Serretti, MD; Andreas Reif, MD; James W. Murrough, MD, PhD; Steven C. Stoner, PharmD; Siu Wa Tang, MD; and Shih-Ku Lin, MD

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Supplementary Table 1. General Principles For Combination Psychopharmacology Prescribing: Achieved Consensus

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
1	In general, the basic notion of combining multiple psychotropic medications for complex or difficult-to-treat psychiatric disorders is an appropriate endeavor in order to achieve remission and optimize tolerability.	55/60 (92%; 82% to 97%)	1/60 (2%)	14/60 (23%)	45/60 (75%)	Personal experience
2	For the majority of patients with uncomplicated, non-treatment resistant psychiatric disorders, prescribers should strive to optimize an appropriate monotherapy before implementing polypharmacy combinations.	55/60 (92%; 82% to 97%)	0/60 (0%)	6/60 (10%)	54/60 (90%)	Literature
3	As a general principle, augmentation pharmacotherapies should not be implemented until the index agent has been fully dose-optimized, unless dose optimization is not feasible due to tolerability limitations, or specific adjunctive agents are needed to target particular symptoms or comorbidities.	58/60 (97%; 88% to 100%)	0/60 (0%)	14/60 (23%)	46/60 (77%)	Personal experience
4	The decision to augment an existing pharmacotherapy after suboptimal response should generally not occur without first confirming (a) diagnostic accuracy, (b) assuring that the initial agent has had adequate adherence, dosing and duration, and (c) unless side effects preclude reaching an adequate dose.	58/60 (97%; 88% to 100%)	1/60 (2%)	11/60 (18%)	48/60 (80%)	Personal experience

5	Combination pharmacotherapies are generally more appropriate than mono-therapies when certain comorbid psychiatric disorders are present (e.g., mood plus another condition such as an anxiety disorder, ADHD, substance use disorders, etc.).	52/60 (87%; 75% to 94%)	3/60 (5%)	22/60 (37%)	35/60 (58%)	Personal experience
6	For difficult-to-treat psychiatric disorders that may involve histories of trauma or signs of a significant personality disorder, introducing a psychotherapy may sometimes be more efficacious than continued augmentations involving pharmacotherapy alone.	54/60 (90%; 80% to 96%)	1/60 (2%)	18/60 (30%)	41/60 (68%)	Personal experience
7	The presence of a highly extensive and elaborate polypharmacology regimen in a patient who remains psychiatrically symptomatic should prompt a rigorous reevaluation of the presumed diagnosis before implementing additional medications for the assumed diagnosis.	58/60 (97%; 88% to 100%)	1/60 (2%)	12/60 (20%)	47/60 (78%)	Personal experience
8	In most cases, the use of 2 atypical antipsychotics in a patient with bipolar disorder should generally be avoided unless it occurs during a cross-titration, an inability to optimize the dose of one antipsychotic, or a history of clinical worsening by using only one antipsychotic.	53/57 (93%; 83% to 98%) 3 abstain	4/60 (7%)	23/60 (38%)	33/60 (55%)	Personal experience
9	In schizophrenia, it is generally preferable to optimize the dose of a single antipsychotic agent before using combinations of antipsychotic medications unless there is a clear rationale or target symptom which	56/56 (100%; 92% to 100%) 4 abstain	3/60 (5%)	15/60 (25%)	42/60 (70%)	Literature

	cannot be addressed via antipsychotic monotherapy, or tolerability obstacles prevent the upward titration of the first agent.			
10	There is generally little if any rationale for combining a first-generation antipsychotic with a second-generation antipsychotic in patients with primary psychotic disorders or psychotic mood disorders unless clear benefit has occurred in an individual patient from such a combination that cannot be achieved via monotherapy.	48/57 (84%; 72% to 92%) 3 abstain	8/60 (13%) 26/60 (43%) 26/60 (43%)	Personal experience
11	In general, if insomnia complaints persist despite multiple medication trials and/or combinations of medications for insomnia, it is preferable to explore other possible explanations for persistent sleep problems rather than continue to devise increasingly elaborate polypharmacy insomnia drug regimens.	57/60 (95%; 86% to 99%)	2/60 (3%) 22/60 (37%) 36/60 (60%)	Personal experience
12A*	If a pharmacotherapy of adequate dose and duration is associated with negligible clinical improvement, switching to another treatment, particularly one having a different mechanism of action, would be preferable to augmentation in most cases.	50/60 (83%; 72% to 91%)	1/60 (2%) 17/60 (28%) 42/60 (70%)	Literature

* “A” designation after item numbers reflects a second-round statement following Round 1 non-consensus on an earlier item version

Supplementary Table 2. Pharmacokinetic and Pharmacodynamic Considerations: Achieved Consensus

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
13	When combining a specific CYP450 inhibitor with a known specific substrate, prescribers should consider whether or not the substrate has a wide therapeutic index; if a drug-drug interaction is theoretically possible, it may have little or no clinical consequences and therefore should not be considered high risk or contraindicated.	47/60 (78%; 66% to 87%)	2/60 (3%)	29/60 (48%)	29/60 (48%)	Pharmacolo-gical rationale
14	When considering potential combinations of psychotropic medications, pharmacogenomic testing often entails costs, limited availability, and interpretative complexity that make its cost–benefit ratio unfavorable in routine practice for minimizing the cumulative burden of adverse effects in most cases, beyond what can be achieved through basic knowledge of drug metabolic pathways and therapeutic drug monitoring (serum drug concentrations).	48/59 (81%; 70% to 89%) 1 abstain	1/60 (2%)	19/60 (32%)	40/60 (67%)	Literature
15	It is reasonable to combine a tricyclic antidepressant with non-TCA drug that inhibits serotonin reuptake for difficult-to-treat cases, with careful attention to pharmacokinetic interactions that could lead to an enhanced side effect burden, cardiac toxicity, or seizures (as when combining clomipramine with fluvoxamine in treatment-resistant OCD), and	47/59 (80%; 68% to 88%) 1 abstain	13/60 (22%)	29/60 (48%)	18/60 (30%)	Personal experience

	TCA doses are informed by therapeutic drug monitoring for safety as well as therapeutic purposes.			
16	It is reasonable, and potentially pharmacodynamically synergistic, to combine a monoamine reuptake inhibitor with a monoamine receptor targeting agent (e.g., mirtazapine as a presynaptic alpha-2 antagonist) or non-SSRI or non-SNRI antidepressants.	46/57 (81%; 67% to 88%) 3 abstain	10/60 (17%) 23/60 (38%) 27/60 (45%)	Literature
17	With the exception of cross-titration (and under rare special circumstances), a combination of two SSRIs, two SNRIs, or an SSRI plus an SNRI should almost always be avoided.	54/60 (90%; 80% to 96%)	1/60 (2%) 16/60 (27%) 43/60 (72%)	Pharmacolo-gical rationale
18	In schizophrenia, when choosing from among antipsychotics that may be deliberately combined, there is generally little if any rationale for combining those with tight binding affinity at the D2 receptor (e.g., risperidone and ziprasidone).	52/57 (91%; 81% to 97%) 3 abstain	3/60 (5%) 31/60 (52%) 26/60 (43%)	Pharmacolo-gical rationale
19	The combination of agents with theoretically opposing effects should generally be avoided such as dopamine antagonists together with dopamine agonists.	45/57 (79%; 66% to 89%) 3 abstain	3/60 (5%) 35/60 (58%) 22/60 (37%)	Pharmacolo-gical rationale
20A*	*In the treatment of either bipolar mania or psychosis in schizophrenia, augmentation of one non-clozapine D2 antagonist with a second non-clozapine D2 antagonist is unlikely to be a beneficial strategy for residual positive symptoms or affective symptoms if optimized*	48/58 (83%; 71% to 91%) 2 abstain	5/60 (8%) 27/60 (45%) 28/60 (47%)	Literature

	dosing of a first agent is either ineffective or poorly tolerated.			

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Supplementary Table 3. Choosing Appropriate (and Avoiding Inappropriate) Augmentation Agents: Achieved Consensus

Question	Item	Strongly Agree (%; 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
21A*	While some literature suggests that adding an MAOI to an existing secondary amine tricyclic antidepressant is safe and can be synergistic in MDD, in practice there is insufficient empirical data and general experience to advise this potentially risky intervention for most patients who are already taking an MAOI.	49/59 (83%; 71% to 91%) 1 abstain	7/60 (12%)	25/60 (42%)	28/60 (47%)	Literature
22A*	Despite limited empirical literature in adults, it is reasonable and safe to combine amphetamine stimulants with alpha agonists (e.g., guanfacine) in difficult to treat forms of adult ADHD, recognizing that such approaches would be lacking an evidence base and anticipated benefits cannot be assured.	37/45 (82%; 68% to 91%) 5 abstain	20/60 (33%)	28/60 (47%)	12/60 (20%)	Pharmacolo-gical rationale
23A*	Despite limited empirical literature, combining amphetamine stimulants with norepinephrine reuptake inhibitors (e.g., atomoxetine or viloxazine) can be possible in specific cases of difficult to treat forms of adult ADHD.	37/45 (82%; 68% to 91%) 5 abstain	21/60 (35%)	34/60 (57%)	5/60 (8%)	Literature
24	It is reasonable to add a stimulant medication such as methylphenidate to an existing regimen to target lethargy, amotivation, or attentional complaints in non-manic, nonpsychotic patients with depression or fatigue.	44/58 (76%; 63% to 85%) 2 abstain	9/60 (15%)	36/60 (60%)	5/60 (25%)	Personal experience

25A*	Adjunctive lithium may, in principle, be an effective antidepressant augmentation in MDD, especially in the presence of symptoms such as suicidal ideation. However, its side effect profile and narrow therapeutic index make it underutilized and underappreciated as an augmentation option compared to many others.	53/60 (88%; 78% to 95%)	1/60 (2%)	17/60 (28%)	42/60 (70%)	Literature
26	In bipolar disorder, lithium has in recent years become an underutilized augmentation therapy that should be given greater consideration as an adjunctive therapy option, especially after the unsuccessful use of one or more other agents.	58/59 (98%; 90%-100%) 1 abstain	2/60 (3%)	7/60 (12%)	51/60 (85%)	Literature
27A*	*Based on the available empirical trials database, adding oxcarbazepine to the polypharmacy regimen of a bipolar disorder patient would be considered an experimental rather than established and evidence-based augmentation approach to target mood symptoms.*	49/56 (88%; 76% to 94%) 4 abstain	5/60 (8%)	22/60 (37%)	33/60 (55%)	Literature
28	Adding gabapentin or pregabalin to the polypharmacy regimen of a bipolar disorder patient may target anxiety, pain or insomnia but is not an appropriate augmentation approach to target mood symptoms.	54/58 (93%; 83% to 98%) 2 abstain	4/60 (6%)	18/60 (30%)	38/60 (63%)	Literature
29	Adding topiramate to the polypharmacy regimen of a bipolar disorder patient may target migraine or appetite suppression but is not an appropriate augmentation approach to target mood symptoms.	51/56 (91%; 80% to 97%) 4 abstain	5/60 (8%)	21/60 (35%)	34/60 (57%)	Literature

30	In nonpsychotic MDD patients with no features suggestive of bipolar disorder, if one chooses to incorporate lamotrigine as an adjunctive pharmacotherapy, it should be acknowledged as an investigational intervention that does not have a robust evidence base for that use.	51/59 (86%; 75% to 93%) 1 abstain	5/60 (8%)	27/60 (45%)	28/60 (47%)	Literature
31A*	Pramipexole is an example of an off label, "repurposed" medication that has shown promise in several preliminary randomized studies offering a potentially efficacious augmentation option to monoaminergic antidepressants for patients with nonpsychotic MDD or bipolar depression.	46/54 (85%; 73% to 93%) 6 abstain	11/60 (18%)	24/60 (40%)	25/60 (42%)	Literature
32	In bipolar disorder, the use of lamotrigine to augment an antimanic mood stabilizer or an atypical antipsychotic would be reasonable to prevent future depression but has low efficacy in the *prevention of future mania/hypomania*.	52/57 (91%; 81% to 97%) 3 abstain	6/60 (10%)	12/60 (20%)	42/60 (70%)	Literature
33	In bipolar I disorder, the use of lamotrigine to augment an antimanic mood stabilizer or an atypical antipsychotic would be appropriate to *prevent future depression.*	53/56 (95%; 85% to 99%) 4 abstain	4/60 (7%)	19/60 (32%)	37/60 (62%)	Literature
34	In bipolar I disorder, the use of lamotrigine to augment an antimanic mood stabilizer or an atypical antipsychotic would be reasonable to *treat current mania or hypomania*.	50/60 (83%); 72% to 91%) [disagree]	5/60 (8%)	18/60 (30%)	37/60 (62%)	Literature
35A*	*In bipolar I disorder, the use of lamotrigine to augment an antimanic mood stabilizer or atypical antipsychotic would not be considered*	51/58 (89%; 77% to 94%) [disagree]	4/60 (7%)	9/60 (15%)	47/60 (78%)	Literature

	a robust strategy specifically to further prevent future mania or hypomania	2 abstain		
36	In bipolar II disorder, the use of lamotrigine to augment an antimanic mood stabilizer or an atypical antipsychotic would be appropriate to target *current depression*.	44/58 (76%; 63% to 85%) 2 abstain	4/60 (7%) 20/60 (33%) 36/60 (60%)	Literature
37A*	*In bipolar II disorder, based on available clinical trials data as well as your own clinical experience, the use of lamotrigine to augment an antimanic mood stabilizer or atypical antipsychotic would be considered a reasonable or robust strategy to prevent future depressions, but not necessarily hypomania.*	52/59 (88%; 77% to 94%) 1 abstain	1/60 (2%) 19/60 (32%) 40/60 (67%)	Literature
38	In bipolar II disorder, the use of lamotrigine to augment an antimanic mood stabilizer or an atypical antipsychotic would be reasonable to *prevent future depression*.	54/58 (93%; 83% to 98%)	5/60 (8%) 24/60 (40%) 31/60 (52%)	Literature
39	In bipolar II disorder, the use of lamotrigine to augment an antimanic mood stabilizer or atypical antipsychotic would be reasonable to treat current hypomania.	46/57 (81%; 69% to 89%) [disagree]	4/60 (7%) 24/60 (40%) 32/60 (53%)	Literature
40	Adding a monoaminergic (e.g., non-glutamatergic) antidepressant to an antipsychotic medication in efforts to target negative symptoms in otherwise stable schizophrenia patients tends to produce only a small and inconsistent benefit, making this approach, in some select situations, a viable but not robust augmentation strategy.	47/54 (87%; 75% to 94%) 6 abstain	11/60 (18%) 33/60 (55%) 16/60 (27%)	Literature
41A*	*If one chose to add either amphetamine or (ar)modafinil to an antipsychotic to target*	52/54 (96%; 87% to 100%)	8/60 (13%) 26/60 (43%) 26/60 (43%)	Literature

	negative symptoms or excessive daytime sedation in an otherwise stable patient with schizophrenia, one must cautiously watch for potential worsening of positive symptoms and also anticipate the possibility of achieving only a small or inconsistent rather than robust and predictable benefit.	6 abstain		
42A*	*There are insufficient data, or adequate firsthand experience to estimate the probability that adding xanomeline-trospium on to a non-anticholinergic antipsychotic drug is likely to have additional benefit over the antipsychotic medication alone.*	37/46 (80%; 66% to 91%) 14 abstain	18/60 (30%) 9/60 (48%) 13/60 (22%)	Literature
43	The simultaneous use of stimulants plus sedative-hypnotics (e.g., benzodiazepines, z-drugs) poses risks for dysregulation of normal circadian wakefulness cycles and should be avoided unless it produced clear benefit that outweighs risks (e.g., for patients with comorbid ADHD plus panic disorder or primary insomnia).	49/57 (86%; 74% to 93%) 3 abstain	9/60 (15%) 29/60 (48%) 22/60 (37%)	Pharmacolo-gical rationale
44	In forms of primary insomnia that do not improve sufficiently with optimized monotherapies, it is reasonable to combine mechanistically non redundant agents (e.g., z-drugs, benzodiazepines, dual orexin receptor antagonists, ramelteon or melatonin).	42/53 (79%; 66% to 88%) 7 abstain	13/60 (22%) 34/60 (57%) 13/60 (22%)	Personal experience
45A*	Routinely adding a sleep aid to an antidepressant for an MDD patient with insomnia is more likely to aid insomnia than to	46/60 (77%; 65% to 86%)	4/60 (7%) 28/60 (47%) 28/60 (47%)	Personal experience

	hasten overall antidepressant response or increase ultimate antidepressant response rates.			

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Supplementary Table 4. Medication Adherence: Achieved Consensus

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
46A*	Clinicians who prescribe multiple psychotropic medications to patients for a psychiatric disorder should anticipate an increased probability of poorer adherence, which may not necessarily simply reflect the consequence of an additive, cumulative side effect burden.	54/60 (90%; 80% to 96%)	1/60 (2%)	16/60 (27%)	43/60 (72%)	Personal experience
47	The addition of a mood stabilizer such as lithium, valproate or lamotrigine to an antipsychotic medication provides inconsistent and insufficient benefit for improving total psychopathology in schizophrenia, making it, in some select situations, a viable but not robust augmentation strategy.	46/55 (84%; 72% to 91%)	7/60 (12%)	35/60 (58%)	18/60 (30%)	Literature

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Supplementary Table 5. When to Augment: Consensus Achieved

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
48	For most if not all psychiatric disorders, there is little rationale for retaining and augmenting a medication if there has been less than a partial response (e.g., >25% improvement from baseline symptom severity in the case of MDD) to that first agent.	49/60 (82%; 70% to 90%)	3/60 (5%)	30/60 (50%)	27/60 (45%)	Personal experience
49	It is reasonable to combine certain medication pairings at the initiation of treatment if supported by adequate efficacy, tolerability and safety data (e.g., olanzapine-fluoxetine combination for either bipolar or treatment-resistant depression) or intended drug-drug interactions (e.g., dextromethorphan-bupropion in major depression).	55/60 (92%; 82% to 97%)	1/60 (2%)	24/60 (40%)	35/60 (58%)	Literature
50	Initiating combination pharmacotherapies may be appropriate and necessary to target specific domains that monotherapies may seldom fully address, or exacerbate, e.g., sleep problems, attentional problems, agitation, impulsivity, or suicidal behavior.	54/60 (90%; 80% to 96%)	3/60 (5%)	25/60 (42%)	32/60 (53%)	Personal experience
51	In major depressive disorder patients who do not improve on complex polypharmacy regimens, strong consideration should be given to undertaking an MAOI trial absent medical contraindications.	54/60 (90%; 80% to 96%)	4/60 (7%)	18/60 (30%)	38/60 (63%)	Literature
52	Rapid cycling bipolar disorder rarely responds to any monotherapy and combinations of	49/57 (86%; 74% to 93%)	6/60 (10%)	24/60 (40%)	30/60 (50%)	Personal experience

	mood stabilizer(s) + atypical antipsychotics represent the preferred treatment approach.	3 abstain		
53	Based on a synthesis of your own clinical experience and understanding of the clinical trials literature, for schizophrenia patients with adequate medication adherence who do not sufficiently improve after several trials of dopamine-blocking antipsychotics and one or two combination-antipsychotic trials, it is preferable to consider a trial of clozapine than to undertake further mono- or combination-antipsychotic trials.	56/57 (98%; 90% to 100%) 3 abstain	2/60 (3%) 11/60 (18%) 47/60 (78%)	Literature

Supplementary Table 6. Polypharmacotherapy and Adverse Effects: Achieved Consensus

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
54	Adding a medication to treat the side effect(s) of an existing pharmacotherapy (e.g., beta blockers to treat tremor, ondansetron to treat nausea, metformin to treat iatrogenic metabolic dysregulation) is only warranted when the existing pharmacotherapy is associated with substantial clinical efficacy not achieved by another therapeutic alternative.	50/60 (83%; 72% to 91%)	2/60 (3%)	24/60 (40%)	34/60 (57%)	Personal experience
55A*	In patients with treatment-adherent but difficult-to-treat schizophrenia or recurrent psychotic mood disorders, if a long-acting injectable (LAI) antipsychotic medication is available and feasible for administration, its use should be prioritized over the use of combinations of oral antipsychotics.	44/59 (75%; 62% to 84%) 1 abstain	5/60 (8%)	16/60 (27%)	39/60 (65%)	Literature

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Supplementary Table 7. Logistics of Augmentation: Achieved Consensus

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
56A*	When augmenting a monoaminergic antidepressant with an additional agent (e.g., a different-class antidepressant, atypical antipsychotic, lithium, thyroid hormone, etc.), while initial signs of response may sometimes be evident in the first 1-2 weeks, it may take 4-6 weeks or even longer before determinations about efficacy can be made.	53/59 (90%; 79% to 96%)	3/60 (5%)	25/60 (42%)	32/60 (53%)	Literature
57	When augmenting a monoaminergic antidepressant with an additional agent (e.g., a different-class antidepressant, atypical antipsychotic, lithium, thyroid hormone, etc.), an adequate trial duration of an augmenting agent is often at least 4-6 weeks in order to fully judge efficacy.	55/60 (92%; 82% to 97%)	4/60 (7%)	27/60 (45%)	29/60 (48%)	Personal experience
58	In most cases, one should not combine an SNRI with a secondary amine tricyclic (e.g., nortriptyline, desipramine) for patients with major depression plus neuropathic pain; optimization of either monotherapy is generally a preferable approach for both conditions.	42/53 (79%; 66% to 88%) 7 abstain	13/60 (22%)	33/60 (55%)	14/60 (23%)	Pharmacologi-cal rationale

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Supplementary Table 8. Concomitant versus Sequential Co-Therapies: Achieved Consensus

Question	Item	Strongly Agree (%, 95% CI)	Confidence			1º Basis for Response
			Low	Medium	High	
59	In patients with nonpsychotic MDD and comorbid well-established ADHD, the decision to sequentially treat one disorder before the other rather than simultaneously treat both disorders is an individualized decision that depends on the severity of each condition.	46/58 (79%; 67% to 88%) 2 abstain	9/60 (15%)	33/60 (55%)	18/60 (30%)	Personal experience
60	In bipolar I disorder patients with comorbid ADHD, use of an established antimanic agent should sequentially always precede initiation of co-therapy with stimulant medications that are meant to target comorbid ADHD symptoms.	57/57 (100%; 93%-100%) 3 abstain	4/60 (7%)	16/60 (27%)	40/60 (67%)	Literature
61	In bipolar II disorder patients with comorbid ADHD, use of an established antimanic agent should sequentially always precede initiation of co-therapy with stimulant medications that are meant to target comorbid ADHD symptoms.	49/58 (84%; 73% to 92%) 2 abstain	5/60 (8%)	30/60 (50%)	25/60 (42%)	Personal experience
62A*	*In patients with a well-established, confirmed diagnosis of ADHD and a comorbid substance use disorder, it is generally most appropriate to treat both conditions simultaneously and not necessarily withhold stimulant medications targeting ADHD symptoms unless there is evidence or history of stimulant misuse or stimulant use disorder.*	41/53 (77%; 64% to 87%) 7 abstain	8/60 (13%)	28/60 (47%)	24/60 (40%)	Literature

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