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Pharmacological Treatment of Bipolar Disorder: Japanese Expert Consensus 2025

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Abstract

Background: Clinical guidelines do not fully address complex treatment scenarios in bipolar disorder. We conducted an updated Japanese expert consensus survey using an innovative two-step design to distinguish broad acceptable therapeutic options from concrete regimen-level priorities across 17 clinical questions (CQs).

Methods: Between October 3 and 17, 2025, 350 psychiatrists jointly certified in neuropsychopharmacology in Japan were surveyed. For each CQ, respondents selected all acceptable medications from a structured list (descriptively categorized as Tier 1 [≥65%], Tier 2 [35%–<65%], or Tier 3 [<35%]) and specified their single preferred regimen via free text.

Results: A total of 159 psychiatrists responded (45.4%). In manic/hypomanic CQs, lithium, valproate, olanzapine, and aripiprazole frequently reached Tier 1; however, aripiprazole monotherapy was the most preferred regimen across all six CQs and the sole Tier 1 agent for perinatal mania. In acute depression, lithium, lurasidone, quetiapine extended-release, and lamotrigine predominated, whereas mixed-features and rapid-cycling CQs were characterized by valproate, lithium, olanzapine, and aripiprazole, with widely dispersed preferred regimens. In maintenance treatment, lithium, aripiprazole, and valproate predominated, with lithium most frequently preferred. Notably, candidate selections and preferred regimens diverged: lemborexant was consistently Tier 2 across all CQs but never ranked among the top three preferred regimens.

Conclusions: The two-step design revealed a meaningful divergence between the breadth of clinically acceptable options and prioritized prescribing regimens. These findings deliver pragmatic, scenario-specific guidance that effectively bridges evidence-based recommendations and real-world clinical decision-making.

1. Introduction

Evidence-based clinical practice guidelines provide essential recommendations for the pharmacological management of bipolar disorder (Keramatian et al. 2023; National Institute for Health and Care Excellence 2025; Ostacher et al. 2025). However, guidelines do not always sufficiently address complex clinical situations encountered in daily practice. Because randomized controlled trials apply rigorous eligibility criteria, the real-world generalizability of their findings remains limited. Moreover, highly consequential clinical scenarios, including mixed features, rapid cycling, older age, and the perinatal period, are challenging to evaluate in clinical trials and are consequently supported by limited high-quality evidence. In these areas, expert consensus can complement guidelines by bridging evidence gaps with pragmatic, clinically grounded recommendations.

Most prior Japanese expert consensus surveys in psychopharmacology, including the 2020 bipolar consensus, utilized nine-point Likert scales to rate predefined treatment strategies, categorizing interventions into first-, second-, and third-line recommendations (Sakurai et al. 2020a, b; Takekita et al.

2026). While this approach effectively quantifies agreement across predefined choices, Likert-based evaluations have inherent methodological constraints. They may not clarify how clinicians select multiple agents and construct real-world monotherapy or combination regimens. Medications broadly considered acceptable or usable in a clinical scenario are not necessarily identical to the single regimen an expert prioritizes as the first-line prescription.

Furthermore, closed-ended formats can bias responses toward the options presented (Converse et al. 2015; Pham et al. 2009; Veloski et al. 2005). Conversely, open-ended responses allow clinicians to express real-world judgment without structural constraints,

capturing nuanced prescribing patterns that closed lists may overlook (O'Cathain and Thomas 2004; Pham et al. 2009). Clinical vignette studies evaluating prescribing behaviors have demonstrated the utility of stepwise formats, in which participants first make a structured selection and subsequently specify their preferred concrete medication via free text (Gidengil et al. 2016).

To update the Japanese expert consensus on bipolar disorder pharmacotherapy, we conducted a nationwide survey employing an innovative two-step response design across 17 clinical questions (CQs). Participants first selected all medications they considered clinically acceptable from a comprehensive structured list, and then entered their single preferred regimen (monotherapy or combination therapy) in free text. By distinguishing the range of acceptable therapeutic options from the concrete regimens experts prioritize in daily practice, this study aimed to update consensus recommendations and contextualize expert prescribing patterns against the 2020 consensus and current clinical practice guidelines.

2. Methods

2.1. Study Design

We conducted a nationwide expert consensus survey between October 3 and October 17, 2025. Following the framework of the 2019 Japanese expert consensus (Sakurai et al. 2020a), an 18-member working group by the Medical Education Committee of the Japanese Society of Clinical Neuropsychopharmacology (JSCNP) developed the CQs based on current clinical practice guidelines for bipolar disorder (Kato et al. 2024). The questionnaire comprised 19 CQs. The primary analysis included 17 pharmacological treatment CQs covering manic or hypomanic episodes, depressive episodes, mixed features, rapid cycling, older adults, perinatal period, and maintenance treatment (Supplementary Table S1; see Additional file 1). The survey additionally included two exploratory items assessing decision factors when selecting long-acting injectable (LAI) antipsychotics and when considering the discontinuation of maintenance pharmacotherapy.

For each of the 17 pharmacological treatment CQs, the working group compiled a comprehensive list of candidate medications. The list included oral and parenteral psychotropic medications approved in Japan, encompassing extended-release and LAI formulations. In contrast to the previous consensus

study that utilized nine-point Likert scales for predefined options (Sakurai et al. 2020a), the current study employed a two-step response design. First, participants selected all medications they considered clinically appropriate or potentially usable for each CQ from the structured list (candidate medications). Second, they specified the prescription regimen they considered optimal for that CQ using free text (preferred regimen). Free-text preferred regimens were unconstrained by the predefined list and could be specified as either monotherapy or combination therapy.

2.2. Participants

We invited 350 psychiatrists specializing in neuropsychopharmacology and jointly certified by the JSCNP and the Japanese Society of Neuropsychopharmacology (JSNP) via email. In this study, these certified psychiatrists were defined as experts. Certification is granted to individuals who meet rigorous criteria, including holding a national medical license and board certification in psychiatry, maintaining membership in either society for at least three years, completing structured training in clinical neuropsychopharmacology at accredited institutions under the supervision of certified instructors, demonstrating academic activity through publications or conference presentations, and successfully passing a standardized certification examination. The survey required approximately 15–30 minutes to complete. Demographics, including years of clinical experience, sex, and workplace location, were recorded. Personally identifiable information collected during eligibility verification was removed before analysis, and all evaluations were performed using an anonymized dataset. This study was approved by the Institutional Review Board of Ehime University Hospital (approval number: 2511004). Questionnaire completion was deemed to constitute informed consent, and the requirement for written consent was formally waived.

2.3. Analysis

Checklist-based candidate medication selections and free-text preferred-regimen responses were analyzed separately for the 17 pharmacological treatment CQs.

For checklist responses, each selected agent was analyzed as a clinically acceptable candidate. We calculated the frequency and proportion of respondents selecting each medication per CQ. We coded options marked as “not selected” as non-selection for the corresponding medication category. Because respondents could choose multiple agents, selection proportions were non-mutually exclusive and could sum to over 100%. The denominator was defined as the number of participants providing valid responses for that CQ. Binomial 95% confidence intervals (CIs) were determined using the Wilson score method. For descriptive categorization, candidate medications were stratified into Tier 1 (highly selected; ≥65%), Tier 2 (moderately selected; 35% to < 65%), or Tier 3 (infrequently selected; <35%). These descriptive tiers summarized selection patterns and were not intended as formal line-of-treatment recommendations comparable to prior Likert-based classifications (Sakurai et al. 2020a).

For free-text preferred-regimen responses, reported regimens were standardized to generic names across brand names, abbreviations, language variants (Japanese and English). Monotherapy and combination regimens were pooled and ranked by frequency, with the top three regimens presented for

each CQ. Regimens listing two or more active substances were classified as combination therapies. Vague or ambiguous entries were reviewed individually and categorized either as unclassifiable or at the pharmacological drug-class level.

Responses to the two exploratory decision-factor items (CQ18, CQ19) were summarized descriptively using frequencies and percentages (Supplementary Table S3; see Additional file 1).

All analyses were descriptive and performed using IBM SPSS Statistics version 30.0 (IBM Co., Armonk, NY, USA) and GraphPad Prism version 8.3.0 for Windows (GraphPad Software, La Jolla, CA, USA). As the survey did not utilize rating scales, no inferential hypothesis testing for treatment-line categorization was conducted.

We used ChatGPT (OpenAI) to assist with English-language writing and editing of the manuscript. All AI-assisted text was reviewed and revised by the authors to ensure accuracy and clarity. The authors take full responsibility for the final content of the manuscript.

3. Results

3.1. Participant Characteristics

A total of 159 of the 350 invited board-certified psychiatrists completed the questionnaire (response rate: 45.4%). The mean duration of clinical experience was 25.7 ± 10.5 years (range, 10–67 years).

3.2. Checklist-Based Candidate Medication Selection

The selection proportions for candidate medications across all CQs are shown in Fig. 1, and detailed rankings for agents ranking within the top 20 are presented in Supplementary Figures S1-S17 (see Additional file 2).

In acute manic episodes in adult men with bipolar I disorder (CQ1), lithium carbonate (96.2%), valproate (94.3%), olanzapine (87.4%), and aripiprazole (82.4%) met Tier 1 criteria. The same four medications reached Tier 1 for adult women with bipolar I mania (CQ2): lithium carbonate (86.2%), aripiprazole (85.5%), valproate (79.9%) and olanzapine (78.6%). For hypomanic episodes in bipolar II disorder, lithium carbonate, valproate, and aripiprazole were Tier 1 candidates in both men (CQ3) and women (CQ4); olanzapine reached Tier 1 in men (70.4%) but fell slightly below the threshold in women (64.2%). For manic episodes during pregnancy and the postpartum period (CQ5), aripiprazole was the sole Tier 1 candidate (84.9%), whereas lithium carbonate (9.4%) and valproate (6.9%) were rarely selected. For manic episodes in older adults (CQ6), aripiprazole (86.8%), valproate (84.9%), olanzapine (69.2%), and lithium carbonate (66.7%) met Tier 1 criteria.

For acute depressive episodes in adults with bipolar I disorder (CQ7, CQ8), and bipolar II disorder (CQ9, CQ10), lithium carbonate, lurasidone, quetiapine extended-release (XR), and lamotrigine consistently met Tier 1 criteria across all four CQs. For depressive episodes in older adults (CQ11), lurasidone (71.7%),

lamotrigine (68.6%), and quetiapine XR (67.3%) were Tier 1 candidates, while lithium carbonate fell into Tier 2 (60.4%). For depressive episodes with anxious distress (CQ12), quetiapine XR (74.8%), lithium carbonate (71.7%), lurasidone (70.4%), and lamotrigine (66.0%) were Tier 1 candidates. In contrast, for depressive episodes with mixed features (CQ13), the Tier 1 candidates were valproate (85.5%), lithium carbonate (80.5%), olanzapine (76.7%), aripiprazole (68.6%), and quetiapine XR (65.4%). For depressive episodes in rapid-cycling bipolar disorder (CQ14), valproate (84.9%), lithium carbonate (76.7%), olanzapine (70.4%), and aripiprazole (69.2%) met Tier 1 criteria. No antidepressant reached Tier 2 or higher in any depression-related CQ.

For maintenance treatment in bipolar I disorder (CQ15) and bipolar II disorder (CQ16), lithium carbonate had the highest selection rate (94.3% and 89.3%, respectively), followed by aripiprazole (82.4% and 73.6%) and valproate (80.5% and 73.6%); all three agents met Tier 1 criteria in both CQs. Lamotrigine was also a Tier 1 candidate in CQ16 (66.7%). For maintenance treatment in rapid cycling (CQ17), valproate (83.6%), lithium carbonate (81.8%), and aripiprazole (78.0%) met Tier 1 criteria.

No anxiolytic or hypnotic reached Tier 1 in any CQ. Among these agents, lemborexant was the most consistently selected, qualifying as Tier 2 across all 17 CQs (selection rate: 40.3%–62.9%). Suvorexant reached Tier 2 in all depression-related CQs (CQ7–CQ14; 35.2%–37.1%). Lorazepam reached Tier 2 in CQ1, CQ2, CQ7, CQ9, CQ12, and CQ13 and had its highest selection rate in CQ12 (43.4%). Comprehensive tier classifications across all medications and CQs are detailed in Supplementary Table S2 (see Additional file 3).

3.3. Free-Text Preferred Regimens

The three most frequently reported preferred regimens for each CQ are summarized in Table 1.

Table 1

Three most frequently preferred regimens derived from free-text responses.

CQ	Scenario	Rank 1 preferred regimen, n (%)	Rank 2 preferred regimen, n (%)	Rank 3 preferred regimen, n (%)
CQ1	Bipolar-I adult men, manic episode	Aripiprazole, 28 (17.6%)	Lithium, 24 (15.1%)	Lithium + Aripiprazole, 21 (13.2%)
CQ2	Bipolar-I adult women, manic episode	Aripiprazole, 49 (30.8%)	Lithium, 19 (11.9%)	Lithium + Aripiprazole, 16 (10.1%); Olanzapine, 16 (10.1%)
CQ3	Bipolar-II adult men, hypomanic episode	Aripiprazole, 45 (28.3%)	Lithium, 42 (26.4%)	Lithium + Aripiprazole, 16 (10.1%)
CQ4	Bipolar-II adult women, hypomanic episode	Aripiprazole, 37 (23.3%)	Lithium, 27 (17.0%)	Olanzapine, 11 (6.9%)
CQ5	Pregnant/postpartum women, manic episode	Aripiprazole, 88 (55.3%)	Olanzapine, 19 (11.9%)	Lamotrigine, 7 (4.4%); Quetiapine, 7 (4.4%); Risperidone, 7 (4.4%)
CQ6	Older adults, manic episode	Aripiprazole, 64 (40.3%)	Lithium, 16 (10.1%)	Olanzapine, 13 (8.2%); Valproate, 13 (8.2%)
CQ7	Bipolar-I adult men, depressive episode	Lurasidone, 40 (25.2%)	Quetiapine, 28 (17.6%)	Lithium, 22 (13.8%)
CQ8	Bipolar-I adult women, depressive episode	Lurasidone, 46 (28.9%)	Quetiapine, 23 (14.5%)	Lithium, 18 (11.3%)
CQ9	Bipolar-II adult men, depressive episode	Lurasidone, 42 (26.4%)	Quetiapine, 30 (18.9%)	Lithium, 21 (13.2%)
CQ10	Bipolar-II adult women, depressive episode	Lurasidone, 43 (27.0%)	Quetiapine, 30 (18.9%)	Lithium, 16 (10.1%)

For each CQ, participants entered in free text the single prescription regimen they considered optimal in clinical practice. Monotherapy and combination regimens were pooled and ranked together by frequency.

*In CQ17, aripiprazole and valproate were tied for second place.

CQ, clinical question.

CQ	Scenario	Rank 1 preferred regimen, n (%)	Rank 2 preferred regimen, n (%)	Rank 3 preferred regimen, n (%)
CQ11	Older adults, depressive episode	Quetiapine, 34 (21.4%)	Lurasidone, 33 (20.8%)	Lithium, 17 (10.7%)
CQ12	Bipolar disorder with anxious distress, depressive episode	Quetiapine, 45 (28.3%)	Lurasidone, 24 (15.1%)	Olanzapine, 13 (8.2%)
CQ13	Bipolar disorder with mixed features, depressive episode	Aripiprazole, 21 (13.2%)	Quetiapine, 20 (12.6%)	Olanzapine, 19 (11.9%)
CQ14	Bipolar disorder with rapid-cycling, depressive episode	Valproate, 18 (11.3%)	Aripiprazole, 17 (10.7%)	Lithium, 15 (9.4%); Quetiapine, 15 (9.4%)
CQ15	Bipolar-I, maintenance treatment	Lithium, 65 (40.9%)	Aripiprazole, 40 (25.2%)	Lithium + Aripiprazole, 15 (9.4%)
CQ16	Bipolar-II, maintenance treatment	Lithium, 52 (32.7%)	Aripiprazole, 28 (17.6%)	Lamotrigine, 17 (10.7%)
CQ17	Bipolar disorder with rapid-cycling, maintenance treatment	Lithium, 34 (21.4%)	Aripiprazole*, 26 (16.4%)	Valproate*, 26 (16.4%)

For each CQ, participants entered in free text the single prescription regimen they considered optimal in clinical practice. Monotherapy and combination regimens were pooled and ranked together by frequency.

*In CQ17, aripiprazole and valproate were tied for second place.

CQ, clinical question.

Across manic and hypomanic CQs (CQ1–CQ6), aripiprazole monotherapy was the most frequently nominated preferred regimen in every CQ, ranging from 17.6% in CQ1 to 55.3% in CQ5. Lithium carbonate ranked second in CQ1–CQ4 and CQ6 but was seldom selected in CQ5. The combination of lithium and aripiprazole ranked third in CQ1–CQ3.

In depression-related CQs (CQ7–CQ14), lurasidone monotherapy was the most frequently preferred regimen in CQ7–CQ10 (25.2%–28.9%), followed by quetiapine and lithium carbonate. Quetiapine ranked first in CQ11 (21.4%) and CQ12 (28.3%). Preferred regimens were markedly more dispersed in mixed features (CQ13) and rapid cycling (CQ14); aripiprazole ranked first in CQ13 (13.2%), whereas valproate ranked first in CQ14 (11.3%).

In maintenance treatment, lithium carbonate was the most preferred regimen across CQ15–CQ17 (21.4%–40.9%). Aripiprazole ranked second in CQ15 and CQ16 (17.6%–25.2%), and tied with valproate for second place in CQ17 (16.4%).

No anxiolytic or hypnotic appeared among the three most frequently reported preferred regimens in any CQ.

3.4. Exploratory Decision Factors

When considering LAI antipsychotics for maintenance treatment (CQ18), “patients’ understanding of relapse prevention” was most frequently identified as the single most critical factor (28.3%). When considering the discontinuation of maintenance pharmacotherapy (CQ19), “duration of clinical stability” was most frequently prioritized as the single most critical factor (32.7%) (Supplementary Table S3; see Additional file 1).

4. Discussion

This nationwide expert consensus survey provides updated, scenario-specific pharmacotherapy patterns in bipolar disorder among Japanese board-certified neuropsychopharmacologists. Our principal findings demonstrate that: (1) in acute mania/hypomania, lithium and SGAs (predominantly aripiprazole) were widely endorsed, with aripiprazole monotherapy emerging as the primary preferred regimen across all scenarios, including perinatal mania; (2) in acute depression, lurasidone, quetiapine XR, lithium, and lamotrigine formed the core options, whereas mixed features and rapid cycling showed distinct profiles centered on valproate, lithium, olanzapine, and aripiprazole, alongside widely dispersed preferred regimens; (3) in maintenance treatment, lithium firmly maintained its status as the most preferred regimen, followed closely by aripiprazole and valproate; and (4) lemborexant was consistently endorsed as a Tier 2 adjunctive option across all clinical phases.

Crucially, candidate medication selections did not necessarily mirror preferred prescribing regimens. The two-step design demonstrated that while the structured checklist captured the clinical breadth of acceptable agents, the free-text responses identified the single regimen experts prioritized in daily practice. This distinction was underscored by the prioritization of aripiprazole monotherapy in mania despite broad lithium endorsement, and by the consistent selection of lemborexant without it ever emerging as a primary preferred regimen. While lithium retained its central foundation as in the 2020 Japanese consensus (Sakurai et al. 2020a), SGA monotherapy has clearly expanded into the preferred first-line choice for acute episodes.

4.1. Manic and Hypomanic CQs

In CQ1–CQ4, candidate selections were centered on lithium, while aripiprazole monotherapy was prioritized when respondents nominated a single concrete regimen. Recent network meta-analyses and systematic review corroborate the robust acute antimanic efficacy of both mood stabilizers (lithium, valproate) and SGAs including aripiprazole (De Prisco et al. 2026; Kishi et al. 2022). The preference for aripiprazole monotherapy in clinical practice may reflect its rapid titration profile, absence of therapeutic drug monitoring requirements, and favorable metabolic and renal tolerability compared with classic mood stabilizers.

In CQ1-CQ3, combination therapy with lithium and aripiprazole ranked third among preferred regimens following monotherapy with either agent. Current Japanese clinical guidelines support mood stabilizers and SGA combinations across acute manic situations (Kato et al. 2024). However, co-treatment confers a greater adverse-event burden than monotherapy (Galling et al. 2015), leading several international guidelines to place monotherapy and combination therapy on equal footing or reserve combination regimens for severe presentations (Jeong et al. 2023; Keramatian et al. 2023). The preference for monotherapy over combination regimens in this survey likely reflects a cautious clinical prioritization of tolerability and safety in routine practice.

Perinatal mania (CQ5) exhibited a distinct pattern: aripiprazole was the sole Tier 1 candidate (84.9%) and the overwhelming preferred regimen (55.3%), whereas lithium (9.4%) and valproate (6.9%) were avoided. Discontinuing pharmacotherapy during pregnancy and the postpartum period markedly increases relapse rates (Wesseloo et al. 2016); hence, maintaining effective pharmacotherapy is strongly recommended (American College of Obstetricians and Gynecologists 2023; Kato et al. 2024). The pronounced consensus for aripiprazole is consistent with pharmacoepidemiological evidence indicating no substantial elevation in overall congenital or cardiac malformations (Huybrechts et al. 2016) and a lower risk of gestational diabetes relative to other SGAs (Park et al. 2018), alongside heightened vigilance regarding valproate teratogenicity and lithium-associated perinatal risks.

4.2. Depression-related CQs

In CQ7-CQ12, lithium, lurasidone, quetiapine XR, and lamotrigine were consistently endorsed as Tier 1 candidates. A recent umbrella review confirmed the efficacy of lurasidone, quetiapine, and olanzapine across response and remission outcomes, with lamotrigine also demonstrating supportive evidence (De Prisco et al. 2026). Notably, while that review identified limited randomized controlled trial support for lithium in acute depression, lithium maintained high candidate selection and preferred-regimen ranking in our study. A nationwide Japanese claims database analysis revealed that both lithium monotherapy and combination therapy were significantly associated with reduced psychiatric hospitalization rates in bipolar disorder (Okumura et al. 2026). Japanese specialists' continued reliance on lithium in depressive episodes may reflect a longitudinal management strategy aimed at mood stabilization, suicide prevention, and hospitalization reduction rather than short-term symptomatic relief alone.

In mixed features (CQ13) and rapid cycling (CQ14), treatment choices diverged sharply from uncomplicated depression: valproate, lithium, olanzapine, and aripiprazole predominated in Tier 1, whereas lurasidone and lamotrigine were selected less frequently. This suggests that clinicians prioritize broader mood stabilization and the prevention of manic destabilization over isolated antidepressant activity. Furthermore, preferred regimens were substantially more dispersed; aripiprazole ranked first in CQ13 (13.2%) and valproate ranked first in CQ14 (11.3%), representing the lowest agreement rates across all 17 CQs. High-level evidence for mixed presentations remains scarce; CANMAT guidelines identified no first-line agents, listing cariprazine and lurasidone as second-line options (Yatham et al. 2021), while Japanese guidelines only conditionally suggest SGAs (Kato et al. 2024). Similarly, rapid cycling is characterized by limited and heterogeneous evidence without an established standard of care

(Strawbridge et al. 2022), although valproate has shown efficacy in smaller clinical trials (Mari et al. 2024; Muzina et al. 2011). The pronounced dispersion in our findings reflects this evidence gap and underscores the clinical challenge of managing these refractory illness courses.

4.3. Maintenance Treatment CQs

Across all maintenance CQs, lithium and aripiprazole achieved Tier 1 candidate status, with lithium consistently ranking first and aripiprazole ranking second among preferred regimens. These findings are supported by international evidence syntheses confirming lithium and aripiprazole as established relapse-prevention therapies (De Prisco et al. 2026).

These patterns indicate that while aripiprazole has consolidated its role as an indispensable maintenance option, lithium remains the gold-standard pillar for long-term prophylaxis in Japanese psychiatric practice.

4.4. Anxiolytic and Hypnotic Agents

A prominent discordance emerged for sleep-targeting agents: lemborexant was consistently selected as a Tier 2 candidate across all 17 CQs, yet never emerged among the top three preferred regimens. Sleep and circadian rhythm disruption occurs across all mood phases of bipolar disorder, exacerbating functional impairment and heralding affective relapse (Tonon et al. 2024). Objective prospective data have linked intra-individual sleep duration variability to depressive recurrence (Esaki et al. 2023), and targeted cognitive behavioral therapy for insomnia in bipolar disorder reduces episode duration and relapse rates (Harvey et al. 2015), validating sleep as a pivotal therapeutic target.

At the same time, controlled trial evidence regarding dual orexin receptor antagonists specifically in bipolar disorder is still accumulating. Although open-label data suggest benefits of lemborexant for insomnia comorbid with mood episodes (Takaesu et al. 2026) and a systematic review supports the tolerability of dual orexin receptor antagonists in psychiatric populations (Kishi et al. 2024), large-scale randomized trials in bipolar disorder are lacking. This explains the observed divergence: Japanese specialists view lemborexant as an appropriate, non-habit-forming adjunctive option to manage sleep disturbances without destabilizing mood, rather than as a primary disease-modifying regimen.

4.5. Exploratory Decision Factors

When selecting an LAI for maintenance therapy, “patients’ understanding of relapse prevention” was the most frequently prioritized consideration. Psychoeducation effectively reduces bipolar recurrence (Bond and Anderson 2015), and illness insight directly correlates with treatment adherence (Yen et al. 2005). This suggests that specialists view LAI initiation not merely as a covert adherence intervention, but as part of a collaborative, shared decision-making process underpinned by psychoeducation.

When considering discontinuation of maintenance pharmacotherapy, “duration of clinical stability” was prioritized most frequently. Discontinuation carries a substantial recurrence risk (Kishi et al. 2021), which is further magnified by residual affective symptoms and sleep disruption (Bai et al. 2026). Prioritizing

sustained stability suggests clinicians seek an extended window of low vulnerability before attempting taper. Nevertheless, the top factors in both items garnered only up to 30% of responses, highlighting that complex maintenance choices cannot be dictated by a single variable and require individualized risk-benefit assessments.

4.6. Strengths and Limitations

This study had several strengths. We surveyed certified psychopharmacologists nationwide, covered 17 comprehensive CQs, and attained a response rate comparable to prior national consensus studies (Sakurai et al. 2020a; Takekita et al. 2026). Methodologically, the two-step design successfully separated broad candidate acceptability from regimen-level prioritization, while the unconstrained free-text field allowed natural reporting of both monotherapies and complex combination strategies.

Several limitations warrant consideration. First, non-response and self-selection biases cannot be excluded. Second, expert consensus represents Level 4 evidence and is intended to complement, not supersede, randomized trials and evidence-based guidelines. Third, presenting the structured checklist prior to the free-text item may have exerted an anchoring effect on preferred regimen choices. Fourth, candidate selection tiers (≥ 65%, 35% to < 65%, < 35%) were descriptive thresholds rather than clinically validated boundaries. Fifth, findings reflect Japanese regulatory approvals and clinical practices, which may limit direct generalizability to other healthcare jurisdictions. Finally, combining pregnancy and the postpartum period into a single CQ pooled two phases with distinct teratogenic, pharmacokinetic, and breastfeeding considerations.

5. Conclusion

This updated Japanese expert consensus provides a comprehensive map of pharmacological decision-making across acute and maintenance phases of bipolar disorder. The two-step design demonstrated that broad candidate acceptability does not directly mirror regimen-level prescribing preferences, successfully distinguishing the therapeutic options clinicians consider viable from those they prioritize in clinical practice. While lithium maintains its central foundation, particularly in maintenance therapy, prescribing preferences prominently featured aripiprazole monotherapy in mania and hypomania, and lurasidone or quetiapine in bipolar depression. These findings deliver pragmatic, scenario-specific clinical guidance that complements evidence-based guidelines and informs real-world psychiatric care.

Abbreviations

CANMAT
Canadian Network for Mood and Anxiety Treatments
CI
confidence interval
CQ
clinical question

JSCNP
Japanese Society of Clinical Neuropsychopharmacology
JSNP
Japanese Society of Neuropsychopharmacology
LAI
long-acting injectable
SGA
second-generation antipsychotic
XR
extended release

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Ehime University Hospital (approval number: 2511004). Questionnaire completion was deemed to constitute informed consent, and the requirement for written consent was formally waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

S. O. has received lecture fees from Sumitomo Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., Otsuka Pharmaceutical Co., Ltd., EA Pharma Co., Ltd., Kowa Company, Ltd. and Eisai Co., Ltd. H. M. has also received speaker's honoraria from Meiji Seika Pharma, Sumitomo Pharma, Otsuka Pharmaceutical, Eisai, Lundbeck, Daiichi Sankyo, Takeda Pharmaceutical, EA Pharma, MSD Pharmaceutical, Viatris Pharmaceutical, Kyowa Pharmaceutical, Shionogi Pharmaceutical, Taisho Pharmaceutical and Mochida Pharmaceutical. H. S. has received grants from Japan Society for the Promotion of Science and honoraria from Viatris, Eisai, Takeda Pharmaceutical, Otsuka Pharmaceutical, Meiji Seika Pharma, Shionogi Pharma, Yoshitomiyakuhin, Sumitomo Pharma, Kyowa Pharmaceutical, Mochida Pharmaceutical, MSD, Daiichi Sankyo, and Lundbeck Japan. Y. T. has received grant funding from the Japan Agency for Medical Research and Development (AMED) and the Japan Society for the Promotion of Science (JSPS). He has also received speaker's honoraria from Meiji Seika Pharma, Sumitomo Pharma, Janssen Pharmaceutical, Otsuka Pharmaceutical, Eisai, Lundbeck, Daiichi Sankyo, Takeda Pharmaceutical, UCB Japan, Novartis, Teijin Pharma, Nippon Boehringer Ingelheim, EA Pharma, and

Mitsubishi Tanabe Pharma, as well as consulting fees from EA Pharma, Otsuka Holdings, IQVIA Japan, and Mitsubishi Tanabe Pharma. H.Tan. has received manuscript or speaker fees from Eisai, Janssen Pharmaceutical, Lundbeck, Otsuka Pharmaceutical, Sumitomo Pharma, Takeda Pharmaceutical, Wiley, and Yoshitomi Yakuhin within the past three years. Y. K. has received speaker's honoraria from Sumitomo Pharma, Otsuka Pharmaceutical, Eisai, Lundbeck, Takeda Pharmaceutical, and EA Pharma. A. K. declares no competing interests. H. Tag. has received honoraria for lectures from Eisai, Janssen Pharmaceutical, Kyowa Pharmaceutical Industry, Lundbeck Japan, Meiji Seika Pharma, MSD K.K., Nippon Boehringer Ingelheim, Otsuka Pharmaceutical, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical, and Viatris. K. S. declares no competing interests. A. N. declares no competing interests. S.H. has received honoraria for lectures from Eisai and Shionogi. T. K. has received honoraria for lectures from Otsuka Pharmaceutical, Sumitomo Pharma, Takeda Pharmaceutical, Lundbeck Japan, and Viatris, and has served as an advisor to Otsuka Pharmaceutical, Aska Pharmaceutical, Takeda Pharmaceutical, and Viatris. H. B. has received research grants from the Japan Agency for Medical Research and Development (AMED) and JSPS KAKENHI; and speaker's honoraria from Otsuka Pharmaceutical, Viatris, Takeda Pharmaceutical, Lundbeck Japan, Meiji Seika Pharma, Towa Pharmaceutical, Shionogi, Daiichi Sankyo, Kowa, Taisho Pharmaceutical, Sumitomo Pharma, Nippon Chemiphar, Nihon Medi-Physics, Mochida Pharmaceutical, Eisai, Kyowa Pharmaceutical, Janssen Pharmaceutical, and Nipro. M. K. has received research grants from the Japan Agency for Medical Research and Development (AMED) and the Ministry of Health, Labour and Welfare (MHLW); consulting fees from Lundbeck, Nippon Chemiphar, Otsuka, Shionogi, Sumitomo Pharma, and Takeda; and honoraria from Eisai, Kyowa Pharmaceutical, Lundbeck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Otsuka, Shionogi, Sumitomo Pharma, Takeda, and Viatris. M.K. also serves as a member of the General Management Committee for the Depression Treatment Guidelines of the Japanese Society of Mood Disorders and as Vice Chairman of its Guideline Development Committee. K. W. received grants from Eisai, Meiji Seika Pharma, Mochida Pharmaceutical, MSD, Otsuka Pharmaceutical, speaker's honoraria from Astra Zeneca, Boehringer Ingelheim, Eisai, Janssen Pharmaceutical, Kyowa Pharmaceutical, Lundbeck Japan, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, MSD, Nippon Chemiphar, Ono Pharmaceutical, Otsuka Pharmaceutical, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical, Teijin Pharma, Viatris, and consulting fees from Boehringer Ingelheim, Daiichi Sankyo, Eisai, Janssen Pharmaceutical, Kyowa Pharmaceutical, Lundbeck Japan, Luye Pharma, Mitsubishi Tanabe Pharma, Nippon Chemiphar, Ono Pharmaceutical, Otsuka Pharmaceutical, Sumitomo Pharma, Takeda Pharmaceutical, and Viatris. K. I. has received personal fees from the following companies over the past three years: Daiichi Sankyo, EA Pharma, Eisai, Eli Lilly Japan, Janssen Pharmaceutical, Kowa, Kyowa Yakuhin Kogyo, Lundbeck Japan, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, MSD, Nexera Pharma, Nippon Boehringer Ingelheim, Nippon Chemiphar, Nipro, Nobelpharma, Novartis Pharma, Ono Pharmaceutical, Otsuka Pharmaceutical, Pfizer Japan, Shionogi, Sumitomo Pharma, Taisho Pharmaceutical, Takeda Pharmaceutical, Viatris, and Yoshitomi Pharmaceutical. N.Y.-F. reports having received honoraria for lectures from Daiichi Sankyo, EA Pharma, Eisai, Eli Lilly and Company, Hisamitsu Pharmaceutical, Janssen Pharmaceuticals, Kowa, Lundbeck, Meiji Seika Pharma, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, MSD, Ono Pharmaceutical, Otsuka Pharmaceutical, Shionogi, Sumitomo Pharma, Takeda Pharmaceutical, Tsumura,

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Authors' contributions

S.O. designed the study, acquired data, conducted statistical analyses, drafted the manuscript, and interpreted the data. H.M. designed the study, acquired data, conducted statistical analyses, and interpreted the data. N.Y.-F., H.S., and J.I. conceptualized the study, designed the study, acquired data, and interpreted the data. Y.T., H.Tan., Y.K., A.K., H.Tag., K.S., A.N., S.H., and T.K. designed the study and acquired data. H.B., M.K., K.W., and K.I. interpreted the data. All authors read and approved the final manuscript.

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References

1. American College of Obstetricians and Gynecologists. Treatment and management of mental health conditions during pregnancy and postpartum: ACOG Clinical Practice Guideline 5. Obstet Gynecol. 2023;141(6):1262–88. https://doi.org/10.1097/AOG.0000000000005202.
2. Bai C, Fan X, Lu W, Wei M, Wu D. Meta-analysis of recurrence rate and influencing factors of bipolar disorder. J Affect Disord. 2026;394. https://doi.org/10.1016/j.jad.2025.120570. Pt B):120570.
3. Bond K, Anderson IM. Psychoeducation for relapse prevention in bipolar disorder: a systematic review of efficacy in randomized controlled trials. Bipolar Disord. 2015;17(4):349–62. https://doi.org/10.1111/bdi.12287.
4. Converse L, Barrett K, Rich E, Reschovsky J. Methods of observing variations in physicians' decisions: the opportunities of clinical vignettes. J Gen Intern Med. 2015;30(Suppl 3):S586–94.

https://doi.org/10.1007/s11606-015-3365-8.

5. De Prisco M, Oliva V, Miola A, Fornaro M, Dragioti E, Croatto G, et al. Evidence based interventions for bipolar disorder across phases and age groups: living umbrella review, evaluation, analysis, and communication hub (U-REACH) project. BMJ. 2026;394:e100216. https://doi.org/10.1136/bmj-2026-100216.
6. Esaki Y, Obayashi K, Saeki K, Fujita K, Iwata N, Kitajima T. Circadian variability of objective sleep measures predicts the relapse of a mood episode in bipolar disorder: findings from the APPLE cohort. Psychiatry Clin Neurosci. 2023;77(8):442–8. https://doi.org/10.1111/pcn.13556.
7. Galling B, Garcia MA, Osuchukwu U, Hagi K, Correll CU. Safety and tolerability of antipsychotic-mood stabilizer co-treatment in the management of acute bipolar disorder: results from a systematic review and exploratory meta-analysis. Expert Opin Drug Saf. 2015;14(8):1181–99. https://doi.org/10.1517/14740338.2015.1053457.
8. Gidengil CA, Linder JA, Beach S, Setodji CM, Hunter G, Mehrotra A. Using clinical vignettes to assess quality of care for acute respiratory infections. Inquiry. 2016;53:0046958016636531. https://doi.org/10.1177/0046958016636531.
9. Harvey AG, Soehner AM, Kaplan KA, Hein K, Lee J, Kanady J, et al. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. J Consult Clin Psychol. 2015;83(3):564–77. https://doi.org/10.1037/a0038655.
10. Huybrechts KF, Hernández-Díaz S, Patorno E, Desai RJ, Mogun H, Dejene SZ, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. JAMA Psychiatry. 2016;73(9):938–46. https://doi.org/10.1001/jamapsychiatry.2016.1520.
11. Jeong JH, Bahk WM, Woo YS, Yoon BH, Lee JG, Kim W, et al. Korean Medication Algorithm Project for Bipolar Disorder 2022: comparisons with other treatment guidelines. Clin Psychopharmacol Neurosci. 2023;21(1):32–48. https://doi.org/10.9758/cpn.2023.21.1.32.
12. Kato T, Ogasawara K, Motomura K, Kato M, Tanaka T, Takaesu Y, et al. Practice guidelines for bipolar disorder by the JSMD (Japanese Society of Mood Disorders). Psychiatry Clin Neurosci. 2024;78(11):633–45. https://doi.org/10.1111/pcn.13724.
13. Keramatian K, Chithra NK, Yatham LN. The CANMAT and ISBD guidelines for the treatment of bipolar disorder: summary and a 2023 update of evidence. Focus (Am Psychiatr Publ). 2023;21(4):344–53. https://doi.org/10.1176/appi.focus.20230009.
14. Kishi T, Matsuda Y, Sakuma K, Okuya M, Mishima K, Iwata N. Recurrence rates in stable bipolar disorder patients after drug discontinuation v. drug maintenance: a systematic review and meta-analysis. Psychol Med. 2021;51(15):2721–9. https://doi.org/10.1017/S0033291720003505.
15. Kishi T, Ikuta T, Matsuda Y, Sakuma K, Okuya M, Nomura I, et al. Pharmacological treatment for bipolar mania: a systematic review and network meta-analysis of double-blind randomized controlled trials. Mol Psychiatry. 2022;27(2):1136–44. https://doi.org/10.1038/s41380-021-01334-4.
16. Kishi T, Koebis M, Sugawara M, Kawatsu Y, Taninaga T, Iwata N. Orexin receptor antagonists in the treatment of insomnia associated with psychiatric disorders: a systematic review. Transl Psychiatry.

2024;14(1):374. https://doi.org/10.1038/s41398-024-03087-4.

17. Mari J, Dieckmann LHJ, Prates-Baldez D, Haddad M, da Silva NR, Kapczinski F. The efficacy of valproate in acute mania, bipolar depression and maintenance therapy for bipolar disorder: an overview of systematic reviews with meta-analyses. BMJ Open. 2024;14(11):e087999. https://doi.org/10.1136/bmjopen-2024-087999.
18. Muzina DJ, Gao K, Kemp DE, Khalife S, Ganocy SJ, Chan PK, et al. Acute efficacy of divalproex sodium versus placebo in mood stabilizer-naive bipolar I or II depression: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2011;72(6):813–9. https://doi.org/10.4088/JCP.09m05570gre.
19. National Institute for Health and Care Excellence. Bipolar disorder: assessment and management. NICE guideline CG185. 2025. https://www.nice.org.uk/guidance/cg185. Accessed 4 Nov 2026.
20. O'Cathain A, Thomas KJ. Any other comments?' Open questions on questionnaires—a bane or a bonus to research? BMC Med Res Methodol. 2004;4:25. https://doi.org/10.1186/1471-2288-4-25.
21. Okumura Y, Tamune H, Harada H, Kato T. Real-world effectiveness of mono- and combination therapies of mood stabilisers and antipsychotics in bipolar disorder: nationwide, within-individual study of 315 046 patients. Br J Psychiatry. 2026;1–9. https://doi.org/10.1192/bjp.2026.10636.
22. Ostacher MJ, Miller CJ, Edwards-Stewart A, Cazares PT, Owen RR, Fuller MA, et al. Synopsis of the 2023 US Department of Veterans Affairs and US Department of Defense clinical practice guideline for the management of bipolar disorder. J Clin Psychiatry. 2025;86(1):24cs15546. https://doi.org/10.4088/JCP.24cs15546.
23. Park Y, Hernández-Díaz S, Bateman BT, Cohen JM, Desai RJ, Patorno E, et al. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. Am J Psychiatry. 2018;175(6):564–74. https://doi.org/10.1176/appi.ajp.2018.17040393.
24. Pham T, Roy C, Mariette X, Lioté F, Durieux P, Ravaud P. Effect of response format for clinical vignettes on reporting quality of physician practice. BMC Health Serv Res. 2009;9:128. https://doi.org/10.1186/1472-6963-9-128.
25. Sakurai H, Kato M, Yasui-Furukori N, Suzuki T, Baba H, Watanabe K, et al. Pharmacological management of bipolar disorder: Japanese expert consensus. Bipolar Disord. 2020a;22(8):822–30. https://doi.org/10.1111/bdi.12959.
26. Sakurai H, Uchida H, Kato M, Suzuki T, Baba H, Watanabe K, et al. Pharmacological management of depression: Japanese expert consensus. J Affect Disord. 2020b;266. https://doi.org/10.1016/j.jad.2020.01.149. :626 – 32.
27. Strawbridge R, Kurana S, Kerr-Gaffney J, Jauhar S, Kaufman KR, Yalin N, et al. A systematic review and meta-analysis of treatments for rapid cycling bipolar disorder. Acta Psychiatr Scand. 2022;146(4):290–311. https://doi.org/10.1111/acps.13471.
28. Takaesu Y, Muraoka H, Takeshima M, Kato M, Hirakawa H, Hori H, et al. A 12-week, open-label, multicenter pilot study to evaluate the efficacy and safety of lemborexant in patients with insomnia

comorbid with depressive episodes (SELENADE). CNS Drugs. 2026;40(3):467–80. https://doi.org/10.1007/s40263-025-01245-w.

29. Takekita Y, Tani H, Kawamata Y, Katsuki A, Muraoka H, Ochi S, et al. Pharmacological treatment of schizophrenia: Japanese Expert Consensus 2025. Schizophrenia (Heidelb). 2026;12(1):70. https://doi.org/10.1038/s41537-026-00770-x.
30. Tonon AC, Nexha A, da Silva MM, Gomes FA, Hidalgo MP, Frey BN. Sleep and circadian disruption in bipolar disorders: from psychopathology to digital phenotyping in clinical practice. Psychiatry Clin Neurosci. 2024;78(11):654–66. https://doi.org/10.1111/pcn.13729.
31. Veloski J, Tai S, Evans AS, Nash DB. Clinical vignette-based surveys: a tool for assessing physician practice variation. Am J Med Qual. 2005;20(3):151–7. https://doi.org/10.1177/1062860605274520.
32. Wesseloo R, Kamperman AM, Munk-Olsen T, Pop VJM, Kushner SA, Bergink V. Risk of postpartum relapse in bipolar disorder and postpartum psychosis: a systematic review and meta-analysis. Am J Psychiatry. 2016;173(2):117–27. https://doi.org/10.1176/appi.ajp.2015.15010124.
33. Yatham LN, Chakrabarty T, Bond DJ, Schaffer A, Beaulieu S, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) recommendations for the management of patients with bipolar disorder with mixed presentations. Bipolar Disord. 2021;23(8):767–88. https://doi.org/10.1111/bdi.13135.
34. Yen CF, Chen CS, Ko CH, Yeh ML, Yang SJ, Yen JY, et al. Relationships between insight and medication adherence in outpatients with schizophrenia and bipolar disorder: prospective study. Psychiatry Clin Neurosci. 2005;59(4):403–9. https://doi.org/10.1111/j.1440-1819.2005.01392.x.

Figures

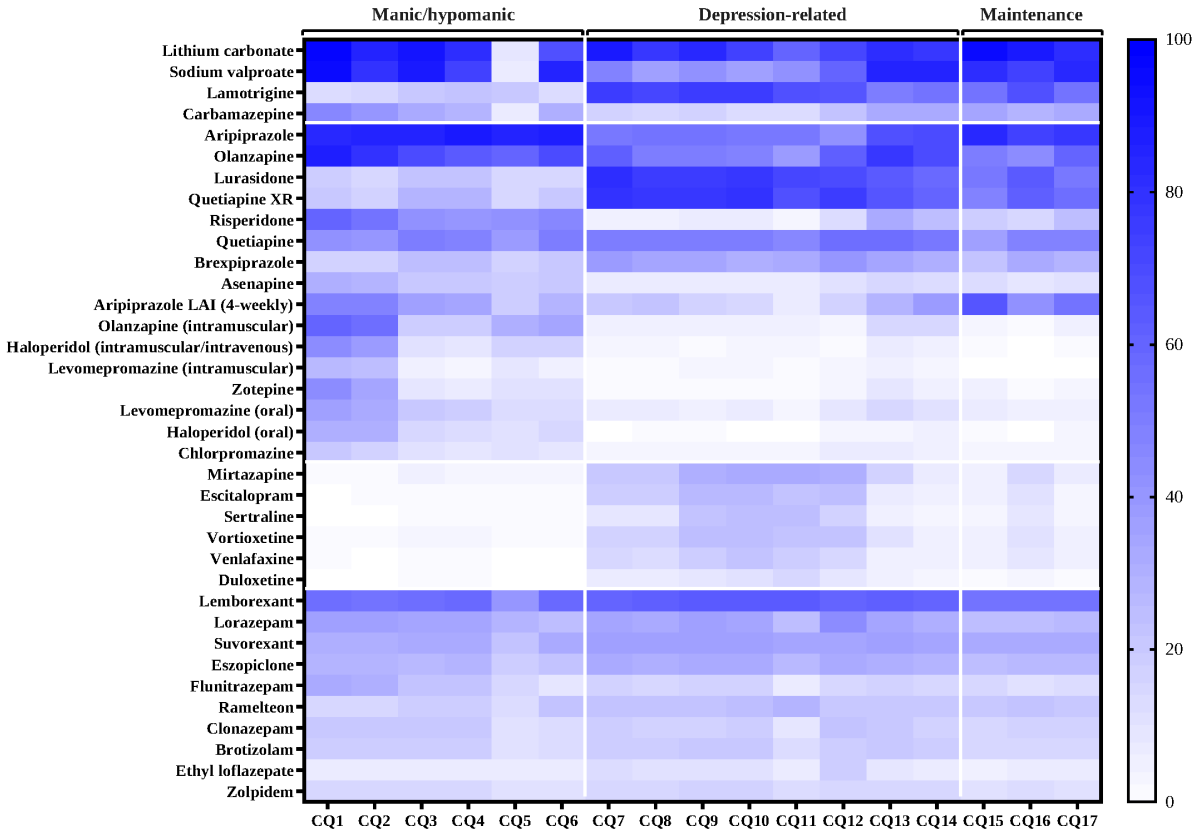

Figure 1

Heatmap of candidate medication selection in clinical questions.

The heatmap displays the percentage of participants who selected each medication as a clinically acceptable candidate for each clinical question (CQ). Multiple medications could be selected for each CQ. Columns are grouped into manic or hypomanic CQs (CQ1-CQ6), depression-related CQs (CQ7-CQ14), and maintenance treatment CQs (CQ15-CQ17). Medications are categorized into mood stabilizers, antipsychotics, antidepressants, and anxiolytics/hypnotics, with horizontal white lines delineating the boundaries between pharmacological classes. Within each class, medications are ordered by their maximum selection percentage across CQ1-CQ17; antipsychotics are further organized by predefined generation- and formulation-based subgroups. The color scale ranges from 0% to 100%.

LAI, long-acting injectable; XR, extended release.

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