Scilight

East West Journal of Psychiatry and Mental Health
https://www.sciltp.com/journals/EWJPMH

Review

Professional Responsibility and Off-Label Prescribing in Psychiatry: An International Framework for Evidence, Consent, and Documented Risk Management

Claudia Libri [1,*], Mario Pinzi [1], Stavroula I. Bargiota [2], Pietro Carmellini [1], Francesco Fargnoli [1] and Giacomo Gualtieri [3]

[1] Department of Molecular Medicine, School of Medicine, University of Siena, 53100 Siena, Italy
[2] Department of Psychiatry, University of Thessaly, 41110 Larissa, Greece
[3] Department of Medicine, Surgery and Neuroscience, University of Siena, 53100 Siena, Italy
* Correspondence: claudialibri@gmail.com

How To Cite: Libri, C.; Pinzi, M.; Bargiota, S.I.; et al. Professional Responsibility and Off-Label Prescribing in Psychiatry: An International Framework for Evidence, Consent, and Documented Risk Management. *East West Journal of Psychiatry and Mental Health* **2026**, *1*(1), 4.

Received: 27 July 2026
Revised: 16 August 2026
Accepted: 1 September 2026
Published: 4 September 2026

Abstract: Off-label prescribing is a structural feature of psychiatric practice because regulatory labels do not always keep pace with evidence, symptom-based treatment needs, multimorbidity, or populations under-represented in registration trials. This narrative comparative review examines how professional responsibility is shaped by regulatory and professional frameworks in Italy, the European Union and Greece, the United States, the United Kingdom, China, Japan, India, and Australia–New Zealand. Across otherwise different systems, five recurring safeguards emerge: an individualized clinical need; explicit consideration of licensed alternatives; a supportable evidentiary rationale; meaningful informed consent; and prospective documentation, monitoring, and reassessment. The authors conceived and drafted the manuscript; OpenAI Codex assisted with language editing, literature/regulatory checks, and formatting; all AI output was reviewed and verified by the authors, who take full responsibility for the content. Greece illustrates how national reimbursement and exceptional-review mechanisms operate within the European setting, while recent Greek pediatric data also show the practical relevance of label gaps. China has moved from a legal grey area to explicit statutory conditions for off-label use, whereas Japan provides a regulatory route for converting well-established clinical knowledge into approved indications. Selected European and US labels for aripiprazole, lurasidone, cariprazine, and brexpiprazole demonstrate that the same evidence can produce different authorized indications across jurisdictions. Off-label status is therefore neither a proxy for poor care nor a guarantee of therapeutic innovation. Professional defensibility depends on the quality, transparency, proportionality, and reversibility of the decision process. A cross-jurisdictional checklist is proposed to support safer psychiatric prescribing without collapsing clinical judgment into mere label compliance.

Keywords: off-label prescribing; psychiatry; professional responsibility; informed consent; psychopharmacology; comparative regulation

1. Introduction

Off-label use means the intentional use of an authorized medicine outside one or more terms of its approved product information, including the indication, age group, dose, route, formulation, or treatment duration. It is distinct from the use of an unlicensed product and from clinical experimentation, although these categories may be conflated in routine discussion [1]. In psychiatry, the label is especially unlikely to map neatly onto clinical

reality: symptom domains cross diagnostic boundaries; patients frequently have medical and psychiatric comorbidity; treatment resistance is common; and children, older adults, pregnant people, and patients with complex presentations have historically been under-represented in registration programs.

US outpatient data show that psychotropic off-label prescribing is substantial and changes over time, while a recent scoping review identifies informed consent, evidence quality, human rights, and professional accountability as the recurrent ethical and legal concerns [2,3]. These findings do not establish that off-label prescribing is inherently inappropriate. A marketing authorization answers a defined regulatory question on a specified dossier; it does not determine every reasonable use in an individual patient. Conversely, pharmacological plausibility, foreign approval, or common practice cannot substitute for a defensible appraisal of benefit, uncertainty, alternatives, and harm.

The central problem is therefore one of governance rather than simple permission. The clinician must know which rule applies locally, distinguish personal prescribing from publicly reimbursed access, and show why the proposed departure from the label is clinically proportionate. The European Commission's comparative study found substantial variation among Member States in policies and practical arrangements for off-label use [4]. That variation matters in psychiatry, where the same prescription can be in-label in one country, off-label but professionally accepted in another, reimbursed only through an exceptional pathway in a third, or subject to institutional review elsewhere.

This review develops the original Italian medico-legal analysis into an East–West and cross-jurisdictional framework suitable for an international psychiatric readership. It has three aims: to compare selected national approaches; to use current psychotropic labels to illustrate regulatory divergence; and to translate convergent principles into a documentation and monitoring framework. It is not legal advice, an exhaustive survey of national law, or a treatment guideline for any particular drug or diagnosis.

2. Methods

A narrative, clinically oriented comparative review was undertaken. Sources were selected through targeted searches of official legislation and regulator or professional-body websites, complemented by PubMed-indexed and peer-reviewed literature. Jurisdictions were chosen to preserve the original focus on Italy while providing an East–West comparison and responding to the journal's international scope: the European Union, Greece, the United States, the United Kingdom, China, Japan, India, and Australia–New Zealand.

Priority was given to primary or authoritative sources: legislation; pages of AIFA, the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the UK General Medical Council (GMC), the Hellenic National Organization for Medicines (EOF), the Chinese government, Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and Australia's Therapeutic Goods Administration (TGA); official product information; systematic or scoping reviews; practice guidelines; and original studies relevant to psychiatry. Secondary legal commentary was used only to clarify publicly available Greek reimbursement provisions. Regulatory pages and product labels were last checked on 23 July 2026, and the literature and regulatory search was updated in August 2026 to capture sources published between 2022 and 2026.

The synthesis was organized around four questions: (1) when may a clinician prescribe outside the label; (2) what evidence, consent, and institutional steps are expected; (3) how are individual clinical freedom and public reimbursement separated; and (4) which documentation practices recur across systems? No meta-analysis, formal risk-of-bias assessment, or exhaustive country ranking was attempted. Legal and regulatory statements are time-sensitive and must be rechecked in the jurisdiction of practice before a clinical or submission decision.

The authors conceived and drafted the manuscript; OpenAI Codex (version not recorded) assisted with language editing, literature/regulatory checks, and formatting; all AI output was reviewed and verified by the authors, who take full responsibility for the content.

3. Why Off-Label Prescribing Is Structural in Psychiatry

Psychiatric prescribing is simultaneously diagnosis-based and domain-based. Agitation, aggression, irritability, suicidality, insomnia, impulsivity, negative symptoms, anxiety, and depressive symptoms occur across multiple disorders, yet registration programs usually target a categorical diagnosis and a defined population. A medicine may therefore have evidence for a clinically important domain without holding the corresponding local indication. Label gaps also arise because obtaining a new indication requires a sponsor, a regulatory dossier, and sufficient commercial or public incentive; older or generic medicines may never receive a formal extension despite sustained clinical use.

The problem is most visible in vulnerable or under-studied populations. In Greece, for example, analysis of 2017 national dispensing data found that about 14% of children and adolescents exposed to psychotropics received at least one medicine whose product information contained no pediatric information; 7.6% received a medicine outside the authorized age range [5]. In India, an earlier tertiary-care outpatient study reported that 39.5% of prescribed medicines were off-label by the British National Formulary used by the investigators, and 79.2% of patients received at least one such prescription [6]; a more recent prospective study in a psychiatry outpatient department found that 417 of 1197 prescribed medicines (34.8%) were off-label, most frequently benzodiazepines such as clonazepam and lorazepam, with depressive disorder the condition most often involved [7]. These studies used different definitions and data sources and should not be compared as if they estimate one common prevalence. The pattern is not confined to any one region: a synthesis of two decades of international data reports that off-label antipsychotic prescribing has remained persistently high, affecting approximately two-thirds of treated youths and 30–60% of treated adults [8], while a 2026 scoping review of 43 studies from 16 countries found that diagnosis- and indication-level factors, particularly disruptive behavior and attention-deficit/hyperactivity disorder, were the drivers most frequently reported for off-label psychotropic use in children and adolescents [9]. Together, these data demonstrate that label mismatch is a practical clinical issue across regions rather than an exclusively European or North American debate.

Off-label use may be reasonable when a licensed option is unavailable, unsuitable, ineffective, or poorly tolerated, but the evidence continuum is broad. At one end is an indication supported by randomized trials, guidelines, or approval by another stringent regulator; at the other is extrapolation from mechanism or anecdote. The evidentiary threshold should rise with uncertainty, vulnerability, invasiveness, expected duration, and severity of possible harm. Severity and the risk of non-treatment also matter: a highly uncertain option may be proportionate in an otherwise refractory, dangerous condition but not for a mild, self-limiting symptom.

4. Comparative Governance across Jurisdictions

4.1. Italy

Italian law expressly frames individual off-label prescribing as an act undertaken under the physician's direct responsibility. Article 3 of Decree-Law No. 23/1998, converted by Law No. 94/1998, permits—in an individual case and after informing the patient and obtaining consent—the use of an authorized medicine for an indication, route, or administration method outside the authorization when the patient cannot be usefully treated with an authorized option and the proposed use is known and consistent with work published in internationally accredited scientific journals [10]. That provision must now be read together with Article 2, paragraphs 348–349, of Law No. 244/2007, which prohibits the treating physician from prescribing a medicine outside its authorized indication where at least favorable phase II clinical-trial data are unavailable for the proposed use, and correspondingly raises the evidentiary threshold applied by AIFA when an off-label use is admitted to publicly funded access under Law No. 648/1996 [11]. Current AIFA information distinguishes this individual route from publicly funded pathways such as Law No. 648/1996 and confirms that individual off-label use may occur even when authorized alternatives exist, but ordinarily at the patient's expense in outpatient care and under the prescriber's responsibility [12]. The statutory framework is therefore one of responsibility rather than of simple permission, and it applies in both private and public health settings; reimbursement, institutional procedures, and contractual arrangements may nonetheless differ. Because the precise relationship between statutory wording, subsequent amendments, reimbursement, and the facts of a case can be complex, local institutional or legal review remains prudent.

The general framework of professional responsibility adds two further layers. Law No. 24/2017 requires healthcare professionals, subject to the specific features of the case, to follow recommendations in recognized guidelines and, in their absence, good clinical care practices [13]. Law No. 219/2017 anchors the therapeutic relationship in free and informed consent and requires understandable information on diagnosis, prognosis, benefits, risks, alternatives, and the consequences of refusal; consent must be documented using an appropriate method [14]. Off-label status does not itself prove negligence, but it intensifies the importance of reconstructing the decision: target symptoms, licensed alternatives, evidence, individualized risk, patient preferences, and a review plan.

4.2. European Union and Greece

At EU level, authorization defines the approved product information, but the act of prescribing and most reimbursement arrangements remain primarily national. Consequently, a centrally authorized product can still be used differently across Member States. The European Commission review documented variation in definitions, professional guidance, reimbursement, and institutional oversight [4]. A foreign or US indication can strengthen the evidentiary context, but it does not automatically alter the EU label or national conditions of lawful use.

Greece provides a useful case study within this shared European regulatory space. Under a 2012 ministerial decision, EOF established a special committee to examine, in exceptional cases, the administration of medicines outside approved indications; requests must be fully documented and submitted through hospitals, the National Organization for Healthcare Services Provision (EOPYY), or other social-insurance bodies [15]. Article 47 of Law 4316/2014, which amended Article 12 of Law 3816/2010, subsequently addressed reimbursement: medicines on the positive list may be prescribed and reimbursed outside their approved indications, combinations, or dosages only where the use forms part of therapeutic protocols based on corresponding international guidelines, proposed by the competent scientific societies and approved through the relevant national process, while outside such protocols reimbursement is confined to exceptional cases documented on an individual basis in accordance with the international literature and following a reasoned request from the health bodies [16]. These mechanisms concern approval and reimbursement pathways; they do not reduce clinical consent and monitoring to administrative formalities. The recent Greek pediatric data further show why national systems need both protection against poorly supported use and routes for clinically justified exceptions [5].

4.3. United States and United Kingdom

In the United States, the FDA regulates the approval and promotion of medicines but generally does not regulate the practice of medicine. Its patient-facing explanation states that healthcare professionals may prescribe an approved drug for an unapproved use when they judge it medically appropriate, while emphasizing that the FDA has not determined that the product is safe and effective for that particular use [17]. This distinction is critical: legality of prescribing does not convert an unapproved use into an FDA-endorsed one, nor does it remove professional duties to evaluate evidence and disclose material uncertainty. This should also be distinguished from the separate restrictions governing manufacturers' promotion of unapproved uses: the clinician's ability to prescribe off-label does not confer a corresponding right on manufacturers to promote an unapproved indication [18].

The UK GMC adopts a needs-based professional standard. Prescribing outside the terms of a UK licence may be necessary when no suitably licensed medicine can meet the patient's needs. The prescriber must be satisfied that there is sufficient evidence or experience to demonstrate safety and efficacy, take responsibility for the prescription, provide appropriate information, monitor the patient, and record the reasons when they are not self-evident [19]. The approach is less a special permission than an explicit extension of ordinary professional accountability.

4.4. China

China's Physician Law, adopted by the Standing Committee of the National People's Congress on 20 August 2021 and in force since 1 March 2022, moved off-label use from a comparatively uncertain legal space into an express statutory framework. The second paragraph of Article 29 permits a physician, in exceptional circumstances such as the absence of an effective or better means of treatment, to adopt a use of a medicine that is not specified in the approved package insert but is supported by evidence-based medical evidence, provided that the patient's express informed consent has first been obtained. Because the provision is keyed to the package insert rather than to the authorized indication alone, it extends to departures in dose, route, and population. The same paragraph further provides that medical institutions shall establish management systems to review the appropriateness of physicians' prescriptions and medication orders and to regulate prescribing conduct strictly [20]. No official English version of the 2021 Law has been identified; renderings here are the authors' translation from the official Chinese text. A Chinese multidisciplinary guideline operationalizes these principles through graded evidence, hierarchical management, consent, adverse-reaction monitoring, and defined responsibilities [21].

Recent analyses show that formal permission alone is not enough. Liang and Cai identified insufficient evidence, defective informed consent, and absent internal review as recurrent sources of liability after the new law [22]. Si and Ma similarly describe the continuing need to align legislation, institutional procedures, and judicial practice [23]. The Chinese experience therefore adds an important East–West lesson: individual therapeutic discretion can coexist with mandatory organizational governance, and documentation quality is a substantive safety mechanism rather than a defensive afterthought.

4.5. Japan

Japan complements case-level off-label practice with a distinctive route for narrowing the gap between clinical knowledge and formal authorization. Through a public knowledge-based application (4ouchi-shinsei), a sponsor may seek approval of a new indication or regimen without conventional additional clinical trials when the use is supported by sufficiently established public knowledge, including authoritative literature and overseas use; PMDA publishes information on the pathway [24]. An assessment of two decades of approvals found that the

mechanism has contributed to authorizing uses already supported by clinical knowledge, although timing and evidence standards remain important [25]. More recent analysis shows how selective the route is in practice: of 171 requests submitted to the responsible review conference between August 2013 and March 2022, 54 were judged to meet the medical-necessity criteria and only 25 were considered eligible for a public knowledge-based application, with the availability of existing domestic treatments and the approval or established-use status of the medicine in the reference Western countries determining the outcome [26]. The pathway therefore narrows the gap without closing it. Analysis of Japan's National Database of Health Insurance Claims indicates that off-label use still accounts for approximately 24% of pediatric inpatient and 14% of pediatric outpatient prescriptions, with wide variation between therapeutic classes [27]. This model shifts part of the burden from repeated individual justification toward regulatory label updating, but it does not remove the need for case-level justification.

4.6. Australia and New Zealand

The Australian TGA describes off-label use of a registered medicine as a clinical decision and generally does not require a TGA exemption, while placing responsibility for the decision and informed consent on the prescriber [28]. In psychiatry, Lehman and Aroney integrated Australian and New Zealand professional, therapeutic-advisory, and indemnity guidance into a decision framework centered on evidence, patient characteristics, consent, documentation, and monitoring [29]. The RANZCP professional practice guideline, revised in 2023, sets out a comparable structure for both countries: it distinguishes prescribing supported by strong evidence, prescribing supported by weaker evidence but consistent with common practice, and experimental use requiring ethics-committee review, and it requires documented informed consent, a recorded rationale and maximum treatment duration, defined indicators of response, therapeutic drug monitoring where available, and peer review or a formal second opinion [30]. Earlier Australian consensus recommendations similarly distinguished routine, evidence-supported off-label use from exceptional or investigational use and linked the degree of oversight to evidence and risk [31].

4.7. Liability and Malpractice Exposure across Jurisdictions

The medico-legal consequences of off-label prescribing differ in form across the jurisdictions reviewed, and off-label status alone should not be treated as a proxy for malpractice [22,23]. In Italy, the statutory framework places the prescribing decision under the physician's responsibility, subjects it to a minimum evidentiary threshold, and links professional accountability to clinical-care standards and informed consent [10,11,13,14]. In the United States, the permissibility of off-label prescribing is distinct from FDA approval, so liability questions remain primarily tied to the clinician's professional duties, the applicable standard of care, informed decision-making, and the facts of the individual case [17]. The UK similarly places emphasis on evidence, professional responsibility, information, monitoring, and documentation [19]. China expressly combines individual duties with mandatory institutional governance, while the Greek and Australian–New Zealand frameworks emphasize documented justification, consent, monitoring, and proportionate oversight [15,20,21,28–31]. Japan provides an additional regulatory route for established uses, potentially reducing reliance on repeated case-by-case justification [24–27]. India is not examined here through a dedicated malpractice-law analysis; its inclusion is therefore limited to the clinical prevalence evidence discussed above [6,7]. Across systems, the more transferable medico-legal lesson is that exposure is likely to turn less on label status in isolation than on whether the prescribing decision was clinically reasonable, evidence-informed, proportionate to risk, adequately communicated, appropriately documented, and followed by monitoring and reassessment [22,30]. This review does not attempt to rank malpractice exposure or provide jurisdiction-specific legal advice. Table 1 compares features of selected off-label governance frameworks.

Table 1. Comparative features of selected off-label governance frameworks.

Jurisdiction	Clinical Permission/Route	Key Safeguards	System-Level Feature
Italy	Individual use under direct physician responsibility; separate AIFA reimbursement/access routes	Individual need, scientific support, information and consent, alternatives, documentation	Law No. 94/1998; Law No. 648/1996 and AIFA pathways
EU/Greece	Prescribing and reimbursement remain nationally organized within EU authorization.	Fully documented exceptional requests; clinical protocols or individual review where applicable	EOF special committee; Greek reimbursement provisions
United States	Approved medicines may generally be prescribed for unapproved uses within medical practice.	Medical appropriateness, evidence appraisal, disclosure of uncertainty, monitoring	FDA approval does not extend to the unapproved use
United Kingdom	Permitted when a licensed medicine cannot meet the patient's needs	Sufficient evidence or experience, responsibility, information, monitoring, reasons recorded	Professional standard set by GMC

Table 1. *Cont.*

China	Expressly permitted under Article 29(2) in exceptional circumstances	Exceptional circumstances (e.g., no effective or better treatment), evidence-based support, prior express consent, mandatory institutional review of prescribing appropriateness	Individual and organizational accountability
Japan	Case-level practice plus a pathway to convert established public knowledge into authorization	Authoritative evidence and regulatory assessment	Public knowledge-based application (kouchi-shinsei)
Australia–New Zealand	Off-label use generally treated as a clinical decision	Evidence, shared decision-making, documentation, monitoring, proportionate committee review	Risk-tiered professional frameworks

5. Regulatory Divergence in Selected Psychotropics

Product labels are useful comparative evidence because they show what a regulator has formally assessed for a defined product, dose, population, and indication. They must nevertheless be read at the level of current product information rather than from memory or a secondary formulary. Table 2 compares selected EMA and FDA indications. It is illustrative, not exhaustive, and does not recommend any listed off-label use.

Aripiprazole is authorized in the EU for schizophrenia and defined bipolar I indications, whereas the US label also includes adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, and Tourette's disorder [32,33]. Lurasidone's EU indication is schizophrenia, while the US label additionally covers depressive episodes associated with bipolar I disorder, including pediatric bipolar depression and adult adjunctive use with lithium or valproate [34,35]. Cariprazine is authorized in the EU for adult schizophrenia; its US indications also include bipolar mania or mixed episodes, bipolar depression, and adjunctive therapy for major depressive disorder [36,37]. Brexpiprazole is authorized in the EU for schizophrenia, including adolescents from 13 years in current product information, while the US label also includes adjunctive treatment of major depressive disorder and agitation associated with dementia due to Alzheimer's disease, with explicit limitations on use [38,39].

These differences have three implications. First, off-label status is jurisdiction- and time-specific. Second, foreign authorization may be relevant evidence but does not displace local law, local product information, or patient-specific appraisal. Third, the responsible question is narrower than whether a drug has ever been approved somewhere: does the foreign evidence meaningfully apply to this patient, formulation, dose, outcome, and risk context?

Table 2. Selected EMA/EU and FDA/US indication differences (verified 23 July 2026).

Medicine	Selected EMA/EU Indication (s)	Additional Selected FDA/US Indication (s)	Interpretive Caution
Aripiprazole	Schizophrenia; defined bipolar I uses	Adjunctive major depressive disorder; irritability associated with autistic disorder; Tourette's disorder	Age, formulation, dose, and indication wording differ.
Lurasidone	Schizophrenia	Bipolar I depression: adult monotherapy; adult adjunctive use with lithium/valproate; pediatric monotherapy	Do not extrapolate automatically across age groups or combinations.
Cariprazine	Adult schizophrenia	Bipolar I mania/mixed episodes; bipolar depression; adjunctive major depressive disorder	US approval does not change the EU indication.
Brexpiprazole	Schizophrenia in adults and adolescents aged 13 years and older	Adjunctive major depressive disorder; agitation associated with dementia due to Alzheimer's disease	US Alzheimer-related indication is not as-needed treatment and retains class warnings Pediatric note: age-specific labeling and authorization should be checked separately in children and adolescents. Where pediatric use is off-label, or evidence is limited, the documentation and monitoring plan should explicitly record the age-specific rationale and the basis for extrapolating evidence.

6. Professional Responsibility: From Permission to Defensibility

6.1. Define the Therapeutic Problem

A defensible record begins with the problem to be treated, not the name of the medicine. The clinician should state the diagnosis where established, the target symptom or functional domain, its severity and duration, previous

interventions, and the foreseeable risk of non-treatment. A dimensional target such as recurrent severe aggression is not self-justifying: its context, triggers, non-pharmacological management, and measurable baseline must be documented.

6.2. Examine Licensed and Non-Pharmacological Alternatives

The record should identify reasonable licensed treatments and explain whether they were ineffective, contraindicated, inaccessible, poorly tolerated, or unsuitable. The explanation should be individualized rather than formulaic. Off-label medication should not become a substitute for indicated psychological, social, environmental, or safeguarding interventions. Equally, persistence with an ineffective licensed treatment solely because it appears regulatorily safer may expose the patient to prolonged illness and avoidable risk.

6.3. Grade the Evidentiary Rationale

The supporting evidence should be described by type and applicability. Regulatory approval in another jurisdiction, high-quality guidelines, systematic reviews, and replicated randomized trials generally carry more weight than uncontrolled series or mechanistic reasoning. Radley and colleagues showed that a large proportion of US off-label prescribing lacked strong scientific support, underscoring the need to distinguish frequency from validity [40]. That gap persists in contemporary practice: a 2026 systematic review of off-label antipsychotic use in children and adolescents with obsessive–compulsive, mood dysregulation, depressive, anxiety, and sleep-related disorders identified only 13 eligible studies, almost all uncontrolled, with no randomized controlled trials, no evidence at all for the sleep or anxiety indications, and GRADE certainty rated very low throughout [41]. Evidence should be matched to population, dose, formulation, comorbidity, co-medication, and outcome. Where evidence is weak, the uncertainty itself must become part of consent, monitoring intensity, and the stopping rule.

To illustrate: the “off-label” use of a psychotropic drug—supported by several consistent clinical studies and a well-characterized adverse-effect profile—may justify a prescription; conversely, an innovative use supported primarily by small observational studies or indirect evidence may warrant a more cautious decision, a more explicit statement of uncertainty, closer early follow-up, targeted adverse-effect surveillance, and a predefined reassessment point and demands even greater caution regarding intensity and risk. In both scenarios, targeted surveillance of adverse effects and intensive monitoring—shared and agreed upon with the patient—are essential. Therefore, the quality of the evidence does not in itself determine the appropriateness of the prescription, but rather helps establish the level of monitoring and review proportionate to the residual uncertainty and clinical risk.

6.4. Make Consent Meaningful

Consent is not a signature detached from the consultation. The patient should receive a comprehensible explanation that the proposed use falls outside the current local authorization; why it is being considered; what evidence and uncertainty exist; which alternatives are available; what benefits are expected; and which adverse effects, interactions, burdens, and monitoring requirements are material. The discussion must be adapted to decisional capacity, language, health literacy, urgency, and the role of carers or legal representatives. In psychiatry, capacity is decision-specific and may fluctuate; the record should distinguish disagreement from incapacity and should revisit consent when circumstances materially change.

In the context of compulsory psychiatric treatment, discussions regarding consent require particular attention, even when the treatment is clinically justified. Clinicians should explain the reasons for “off-label” use and any significant potential risks in understandable terms, while documenting the patient’s questions and preferences whenever possible. Even greater caution should be exercised in compulsory treatment settings, given the patient’s vulnerability and the associated risks regarding the clinician’s professional liability. Clinical documentation must clearly and unequivocally set out the scientific and clinical basis for the treatment and the rationale behind the choice, as well as specify the clinical targets, the failure of previous treatments, and the alternatives considered.

6.5. Prespecify Monitoring and Reversibility

In the case of long-term off-label psychotropic treatment, gradual discontinuation of the medication (deprescribing) should be considered a clinical decision forming part of a careful and complex decision-making process. Dosage reduction may need to be gradual and personalized to avoid the onset of discontinuation or withdrawal symptoms, particularly if these overlap with a flare-up of the underlying condition. Clinical documentation should clearly outline the discontinuation regimen, specifying the symptoms to monitor, the planned reduction schedule, and the necessary clinical and laboratory monitoring protocols.

A therapeutic trial should have observable targets and a time horizon. Monitoring must reflect both the drug and the off-label context: symptom change, functioning, suicidality or behavioral risk where relevant, adverse effects, physical observations, laboratory measures, interactions, adherence, and patient-reported experience. The plan should define when benefit will be reviewed, what constitutes failure or unacceptable harm, and how the drug will be reduced or stopped when appropriate. Long-term continuation deserves a new justification rather than automatic renewal.

6.6. Use Proportionate Institutional Oversight

Not every evidence-supported routine off-label prescription requires a committee, but novelty, weak evidence, high toxicity, vulnerable populations, coercive settings, substantial cost, or repeated institutional use may justify pharmacy, therapeutics, ethics, or specialist review. China's statutory model, Greece's exceptional committee route, and Australian–New Zealand risk-tiered frameworks show different ways to distribute responsibility beyond the individual prescriber [15,21,28,30]. Institutions should maintain searchable policies, facilitate pharmacovigilance, and periodically review repeated off-label uses that may warrant a protocol or regulatory update. Table 3 reports Minimum documentation and review checklist for psychiatric off-label prescribing.

Table 3. Minimum documentation and review checklist for psychiatric off-label prescribing.

Step	Minimum Record	Escalation Prompt
1. Clinical target	Diagnosis, target domain, severity, functional impact, urgency, risk of non-treatment	Unclear target, coercive setting, or rapidly changing risk
2. Alternatives	Licensed and non-pharmacological options tried, contraindicated, unavailable, or unsuitable.	Reasonable authorized option not yet assessed.
3. Evidence	Guidelines, regulatory documents, trials/reviews, applicability and limitations	Single weak source, major extrapolation, or novel combination
4. Proportionality	Expected benefit, foreseeable harms, vulnerability, comorbidity, interactions, patient priorities	High toxicity, pregnancy, childhood, frailty, impaired capacity
5. Consent	Off-label status, rationale, alternatives, uncertainty, risks, monitoring, opportunity for questions	Capacity concern, disagreement among representatives, language barrier
6. Trial plan	Dose, duration, measurable outcomes, follow-up timing, stopping/tapering criteria	No measurable outcome or open-ended continuation
7. Monitoring	Clinical, physical and laboratory measures; adverse-event reporting; adherence and experience	Emerging safety signal or monitoring unavailable
8. Reassessment	Benefit–harm review, renewed consent when material facts change, decision to continue/modify/stop	Repeated use suggests need for institutional protocol.

Note: The eight documentation steps are intended to be applied proportionately rather than as a uniformly burdensome checklist. For low-risk, well-established off-label uses supported by substantial clinical evidence, documentation may be concise while still recording the clinical target, rationale, relevant alternatives, informed decision, and an appropriate monitoring plan.

7. Discussion

The comparison reveals convergence beneath regulatory diversity. Italy articulates direct physician responsibility in statute; Greece adds exceptional review and reimbursement mechanisms; the United States separates FDA approval from medical practice; the UK uses a professional needs-and-evidence standard; China combines explicit permission with institutional governance; Japan offers a route for regulatory recognition of established public knowledge; and Australia–New Zealand emphasize risk-tiered decision support. Across these systems, the recurring elements are necessity or patient benefit, evidence, informed participation, documentation, monitoring, and accountability.

This convergence supports a position that is neither permissive nor label-absolutist. A label is a central safety and regulatory document, but it is not a complete map of psychiatric therapeutics. Treating any departure as improper ignores evidence evolution and unmet need; treating any plausible use as innovation ignores uncertainty, promotion risks, polypharmacy, and the vulnerability of many psychiatric patients. The ethical and professional quality of off-label prescribing lies in the process connecting the patient's need to the evidence and making that connection open to review.

The East–West comparison also identifies potentially transferable policies. China's institutional review requirement is relevant to hospitals where repeated high-risk uses can otherwise remain invisible. Japan's public knowledge-based application suggests a way to convert mature evidence into formal labeling instead of perpetually shifting responsibility to individual clinicians. Greek reimbursement and committee procedures show the importance—and the complexity—of separating clinical permissibility from public funding. Australia–New Zealand frameworks demonstrate how oversight can be scaled rather than imposed uniformly. European systems

could benefit from clearer shared evidence summaries and mechanisms for non-commercial indication updates, while all systems need stronger research inclusion of pediatric, geriatric, pregnant, and multimorbid populations.

Documentation should not be reduced to defensive medicine. A well-constructed record improves care continuity, supports deprescribing, enables audit, and makes changing evidence actionable. Conversely, a generic consent form cannot cure a weak rationale, and a cited paper cannot compensate for absent follow-up. The practical unit of quality is the complete decision cycle: target, alternatives, evidence, consent, trial, monitoring, and reassessment.

This review has limitations. It is narrative rather than systematic; jurisdictions were purposively selected; legal sources were reviewed in their available language or official/verified summaries; and national law, reimbursement, product information, and professional guidance change over time. The selected drug-label comparison captures only a few antipsychotics and does not assess comparative efficacy. Country-level prevalence studies use different definitions and cannot be pooled. Finally, the manuscript offers a professional framework, not patient-specific treatment advice or a substitute for local legal consultation.

8. Conclusions and Future Perspectives

Off-label prescribing is an enduring component of psychiatric care, but its legitimacy cannot be inferred from prevalence, novelty, foreign approval, or clinical habit. It becomes professionally defensible when an individualized need is linked to the best applicable evidence; licensed and non-pharmacological alternatives are considered; material uncertainty is communicated; consent is meaningful; outcomes and harms are monitored; and continuation remains reversible and reviewable.

The international comparison suggests that patient protection and therapeutic freedom are not opposing goals. Both improve when clinicians are supported by current product information, accessible evidence summaries, risk-proportionate institutional review, and pathways that translate mature off-label evidence into formal indications. For psychiatry, the next policy step is not to eliminate off-label use, but to make every such decision more transparent, equitable, auditable, and capable of learning from outcomes across health systems.

Author Contributions

Conceptualization, C.L.; methodology, C.L. and G.G.; literature search and regulatory-source verification, C.L., M.P., S.I.B.; comparative analysis, C.L., M.P., S.I.B., F.F., P.C.; writing—original draft preparation, C.L.; writing—review and editing, C.L. and G.G.; supervision, F.F., P.C. All authors have read and agreed to the published version of the manuscript.

Funding

This manuscript was supported by, and informed by the scientific framework developed within, the OPADE project. The OPADE project received funding from the European Union's Horizon Europe research and innovation program under grant agreement no. 101095436. While no OPADE dataset was used directly in the present manuscript, the project informed its background and rationale. The OPADE study is registered at ClinicalTrials.gov (NCT06550037), and its published protocol is cited as relevant background literature.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

During manuscript preparation, the authors conceived the manuscript, wrote the outline, and drafted the first version. OpenAI Codex (version not recorded) was used to assist with English-language editing, comparative

literature and regulatory-source checking, and document formatting. The authors critically reviewed every AI-generated output, reviewed and edited the final manuscript, verified every statement and reference, and took full responsibility for the submitted content.

References

1. Wittich, C.M.; Burkle, C.M.; Lanier, W.L. Ten Common Questions (and Their Answers) about Off-Label Drug Use. *Mayo Clin. Proc.* **2012**, *87*, 982–990. https://doi.org/10.1016/j.mayocp.2012.04.017.
2. O'Brien, P.L.; Cummings, N.; Mark, T.L. Off-Label Prescribing of Psychotropic Medication, 2005–2013: An Examination of Potential Influences. *Psychiatr. Serv.* **2017**, *68*, 549–558. https://doi.org/10.1176/appi.ps.201500482.
3. dos Santos, H.M.M.; Botelho-Souza, L.F.; Nunes, R.; et al. Thematic Mapping of Off-Label Prescription in Psychiatry and Its Implications for Bioethics, Human Rights, and Clinical Practice: A Scoping Review. *Front. Psychiatry* **2026**, *17*, 1705340. https://doi.org/10.3389/fpsyt.2026.1705340.
4. European Commission. Study on Off-Label Use of Medicinal Products in the European Union. Available online: https://health.ec.europa.eu/document/download/8fbaaf48-32ce-4191-98c6-cfb76e783d47_en (accessed on 23 July 2026).
5. Pesiou, S.; Barcelo, R.; Papazisis, G.; et al. Prevalence of Use of On-Label and Off-Label Psychotropics in the Greek Pediatric Population. *Front. Pharmacol.* **2024**, *15*, 1348887. https://doi.org/10.3389/fphar.2024.1348887.
6. Kharadi, D.; Patel, K.; Rana, D.; et al. Off-Label Drug Use in Psychiatry Outpatient Department: A Prospective Study at a Tertiary Care Teaching Hospital. *J. Basic Clin. Pharm.* **2015**, *6*, 45–49. https://doi.org/10.4103/0976-0105.152090.
7. Gadaria, S.; More, S.A.; Pal, V.S.; et al. A Prospective Observational Study on the Off-Label Use of Medications in the Psychiatry Outpatient Department of a Tertiary Care Hospital. *Indian J. Pharmacol.* **2026**, *58*, 96–100. https://doi.org/10.4103/ijp.ijp_184_25.
8. Verdoux, H. Antipsychotic Off-Label Use in the 21st Century: An Enduring Public Health Concern. *Dialogues Clin. Neurosci.* **2025**, *27*, 1–12. https://doi.org/10.1080/19585969.2025.2449833.
9. Tanana, L.; Harrison, C.; Nishtala, P.S.; et al. Factors Associated with the Off-Label Use of Psychotropic Medicines in Children and Adolescents: A Scoping Review. *Aust. N. Z. J. Psychiatry* **2026**, *Epub ahead of print*. https://doi.org/10.1177/00048674261475163.
10. Italian Republic. Law 8 April 1998, No. 94: Conversion, with Amendments, of Decree-Law 17 February 1998, No. 23; Official Gazette, General Series No. 86, 14 April 1998. Available online: https://www.gazzettaufficiale.it/eli/id/1998/04/14/098G0128/sg (accessed on 23 July 2026).
11. Italian Republic. Law 24 December 2007, No. 244, Article 2, Paragraphs 348–349; Official Gazette, General Series No. 300, 28 December 2007, Ordinary Supplement No. 285. Available online: https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:2007-12-24;244 (accessed on 31 August 2026).
12. Italian Medicines Agency. Early Access and Off-Label Use. Available online: https://www.aifa.gov.it/en/accesso-precoce-uso-off-label (accessed on 23 July 2026).
13. Italian Republic. Law 8 March 2017, No. 24, Article 5: Clinical-Care Good Practices and Guideline Recommendations. Available online: https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:2017-03-08;24~art5= (accessed on 23 July 2026).
14. Italian Republic. Law 22 December 2017, No. 219, Article 1: Informed Consent. Available online: https://www.normattiva.it/uri-res/N2Ls?urn:nir:stato:legge:2017-12-22;219!vig= (accessed on 23 July 2026).
15. Hellenic Republic, Ministry of Health. Ministerial Decision ΔΥΓ3(α)/οικ.Γ.Υ.154 of 29 February 2012: Medicinal Products Outside Approved Indications; Government Gazette (ΦΕΚ) Β′ 545/1 March 2012. Official text available from the National Printing House. Available online: https://search.et.gr/el/fek/?fekId=476939 (accessed on 31 August 2026).
16. Hellenic Republic. Law 4316/2014, Article 47: Coverage of Medicines Outside Approved Indications, amending Article 12(1)(a) of Law 3816/2010; Government Gazette (ΦΕΚ) Α′ 270/24 December 2014. Official text available from the National Printing House. Available online: https://www.taxheaven.gr/law/4316/2014 (accessed on 31 August 2026).
17. U.S. Food and Drug Administration. Understanding Unapproved Use of Approved Drugs: Off-Label. Available online: https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label (accessed on 23 July 2026).
18. U.S. Food and Drug Administration. Communications from Firms to Health Care Providers regarding Scientific Information on Unapproved Uses of Approved/Cleared Medical Products: Questions and Answers. Guidance for Industry. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/communications-firms-health-care-providers-regarding-scientific-information-unapproved-uses (accessed on 23 July 2026).
19. General Medical Council. Prescribing Unlicensed Medicines. Available online: https://www.gmc-uk.org/professional-standards/the-professional-standards/good-practice-in-prescribing-and-managing-medicines-and-devices/prescribing-unlicensed-medicines (accessed on 23 July 2026).

20. People's Republic of China. Physician Law of the People's Republic of China, Article 29; adopted by the Standing Committee of the National People's Congress on 20 August 2021, in force 1 March 2022 (Presidential Order No. 94) (in Chinese). Available online: http://www.npc.gov.cn/npc/c2/c30834/202108/t20210820_313104.html (accessed on 31 August 2026).
21. Zuo, W.; Sun, Y.; Liu, R.; et al. Management Guideline for the Off-Label Use of Medicine in China (2021). *Expert Rev. Clin. Pharmacol.* **2022**, *15*, 1253–1268. https://doi.org/10.1080/17512433.2022.2120468.
22. Liang, S.; Cai, F. Off-Label Drug Use in China after the Physician Law (2021): Legal Challenges and Solutions. *Front. Pharmacol.* **2025**, *16*, 1547418. https://doi.org/10.3389/fphar.2025.1547418.
23. Si, W.; Ma, P. Judicial and Legislative Practice and Related Suggestions on Off-Label Drug Use in China. *BMC Health Serv. Res.* **2023**, *23*, 312. https://doi.org/10.1186/s12913-023-09293-y.
24. Pharmaceuticals and Medical Devices Agency. Public Knowledge-Based Applications for Prescription Drugs. Available online: https://www.pmda.go.jp/review-services/drug-reviews/review-information/p-drugs/0016.html (accessed on 23 July 2026).
25. Maeda, H.; Fukuda, Y.; Uchida, M. Assessment of Drugs Approved by Public Knowledge-Based Applications (Kouchi-Shinsei) during the Last Two Decades in Japan. *Clin. Pharmacol. Ther.* **2021**, *110*, 1127–1135. https://doi.org/10.1002/cpt.2332.
26. Hinomura, A.; Obata, D.; Matsubayashi, J.; et al. Facts and Issues of Submitting Applications (Public Knowledge-Based Applications) for Unapproved and Off-Label Drugs with High Medical Needs in Japan. *Curr. Ther. Res.* **2026**, *104*, 100819. https://doi.org/10.1016/j.curtheres.2025.100819.
27. Aino, S.; Nanbu, S.; Narukawa, M. Pediatric Off-Label Use in Japan: Insights from the National Database of Health Insurance Claims. *Pediatr. Int.* **2026**, *68*, e70319. https://doi.org/10.1111/ped.70319.
28. Therapeutic Goods Administration. Supply an Unapproved Therapeutic Good (Sponsors). Available online: https://www.tga.gov.au/products/unapproved-therapeutic-goods/access-pathways/supply-unapproved-therapeutic-good-sponsors (accessed on 23 July 2026).
29. Lehman, K.; Aroney, E. A Guided Framework for Assessing Off-Label Medication Use in Psychiatry. *Australas. Psychiatry* **2024**, *32*, 63–67. https://doi.org/10.1177/10398562231211168.
30. Royal Australian and New Zealand College of Psychiatrists. Professional Practice Guideline 4: 'Off-Label' Prescribing in Psychiatry, Version 4.0. Available online: https://www.ranzcp.org/getmedia/edc66b1d-005b-411d-b277-5c7fddc71ba2/ppg-4-off-label-prescribing-december-2023.pdf (accessed on 31 August 2026).
31. Gazarian, M.; Kelly, M.; McPhee, J.R.; et al. Off-Label Use of Medicines: Consensus Recommendations for Evaluating Appropriateness. *Med. J. Aust.* **2006**, *185*, 544–548. https://doi.org/10.5694/j.1326-5377.2006.tb00689.x.
32. European Medicines Agency. Abilify: EPAR—Product Information. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/abilify (accessed on 23 July 2026).
33. U.S. Food and Drug Administration. Abilify (Aripiprazole) Prescribing Information. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/021436s046s050lbl.pdf (accessed on 23 July 2026).
34. European Medicines Agency. Latuda: EPAR—Product Information. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/latuda (accessed on 23 July 2026).
35. U.S. Food and Drug Administration. Latuda (Lurasidone Hydrochloride) Prescribing Information. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/200603s041lbl.pdf (accessed on 23 July 2026).
36. European Medicines Agency. Reagila: EPAR—Product Information. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/reagila (accessed on 23 July 2026).
37. U.S. Food and Drug Administration. Vraylar (Cariprazine) Prescribing Information. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/204370s014s015s016s017lbl.pdf (accessed on 23 July 2026).
38. European Medicines Agency. Rxulti: EPAR—Product Information. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/rxulti (accessed on 23 July 2026).
39. U.S. Food and Drug Administration. Rexulti (Brexpiprazole) Prescribing Information. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/205422s014lbl.pdf (accessed on 23 July 2026).
40. Radley, D.C.; Finkelstein, S.N.; Stafford, R.S. Off-Label Prescribing among Office-Based Physicians. *Arch. Intern. Med.* **2006**, *166*, 1021–1026. https://doi.org/10.1001/archinte.166.9.1021.
41. Holopainen, A.K.; Vainiotalo, P.A.; Arrhenius, B.P.; et al. Systematic Review: Efficacy of Off-Label Antipsychotic Use in Children and Adolescents with Obsessive-Compulsive, Mood Dysregulation, Depression, Anxiety, and Sleep-Related Disorders. *Eur. Child Adolesc. Psychiatry* **2026**, *Epub ahead of print*. https://doi.org/10.1007/s00787-026-03049-9.