

# Off-label Drug Prescribing: Deciphering the Ambiguity

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## ABSTRACT

The term off label prescribing refers to use of a drug in a manner not approved by the regulatory authorities. The term also applies to the use of a marketed medication in a patient population, dosage, or dosage form that does not have regulatory approval. The practice of off label prescribing is widespread and is seen in almost all branches of medicine. The usage may be supported by strong scientific evidence and research but it does not guarantee the safety of the drug in a large population. Therefore this review focusses on usage of off label medications in different fields of medicine, the possible reason for the use and possible benefits and harms of off label prescribing

**Keywords:** Off-label Drug, Deciphering the Ambiguity

## OFF LABEL DRUG PRESCRIBING: AN INSIGHT

The off label use of medicines refers to the prescription of a medication in a manner different from that approved by the regulatory authorities such as US-FDA or CDSCO. It includes the usage of pharmaceutical product for an indication, age group, dosage, or route of administration that is not approved by the authorities. Although off label use of pharmaceutical product has not been formally evaluated but Off-label prescribing is considered to be legal as long as it does not violate the safety standards or the ethical guidelines. The practice of off label prescribing is common in almost all branches of medicine, it has been estimated that 40% of the all the drugs prescribed in adults are considered to be off label. A much higher rate (about 90%) of off label prescribing is seen in pediatric patients. 24% of all drugs prescribed in pregnancy are considered to be off label.<sup>1,2</sup> This high rate of off label prescribing is likely to be encountered in pregnant females and children since most clinical trials are not performed in this subset of population due to ethical concerns.

It is however observed that the off label prescribing is not always supported by strong scientific evidence. In an examination of off-label prescribing of 160 commonly prescribed drugs, off-label use was also found to account for 21% of all prescriptions, and most off-label drug uses (73%) were shown to have little or no scientific support<sup>3</sup>

Therefore, the idea of this review article is to focus on off label prescribing in different fields of medicine, we tried to gather information regarding different drugs that are frequently prescribed in an off-label manner.

## OFF LABEL PRESCRIBING IN MEDICAL PSYCHIATRY

The prescription of psychotropic medicines across all age

groups is rising worldwide and not just by Psychiatric Physicians but also by general physicians. It has been observed that 45.1% patients receiving psychiatric medications in general hospitals were off label and that most frequently prescribed medications were Benzodiazepines (25.8%) followed by atypical antipsychotics (18.2%) and typical antipsychotics (17.2%).<sup>4</sup>

A similar trend of prescribing was also observed in India. Majority of patients attending the psychiatric OPD were prescribed the off label drugs (39.5%) and the most frequently used drugs in off-label manner were clonazepam (12.4%), lorazepam 30 (12%), and trihexyphenidyl HCL (10%).<sup>5</sup>

A higher incidence of Insomnia in most psychiatric patients warranted the higher overall use of Benzodiazepines. Drugs such as clonazepam, lorazepam are used in depression, mania, bipolar disorder, obsessive compulsive disorder in off label manner as these drugs provide a calming effect to the patients and prevent acute manic episodes. Antipsychotics were the next most commonly prescribed off label drugs for depression and bipolar affective disorders, dementia, anxiety disorders, alcohol and drug dependence, personality disorder, post-traumatic stress and pervasive developmental disorders. Other off label drugs in psychiatry include anticonvulsants such as Sodium valproate and Carbamazepine prescribed as Mood stabilizers in mania and schizoaffective disorder.<sup>6</sup> Use of anti-depressants such as selective serotonin reuptake inhibitors (SSRI's) for non-mood disorders is not uncommon as it has been observed that more than 40% of prescriptions anti-depressants have an off label indications such as eating disorders, phobias or anxiety related disorders.

## OFF LABEL PRESCRIBING IN ANESTHESIOLOGY

Drug prescribing in anesthesiology are broadly categorized as Anesthetic agents, adjuvants and supportive drugs. A study conducted on 400 patients of anesthetic ward in India revealed that 20.19% of the overall drugs prescribed were

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off-label. 46.26% of these drugs were classified as off label as these were used in dosage other than approved and 33.29% drugs were used in conditions other than approved.

Ramosestron was most commonly prescribed for post-operative nausea and vomiting, which is its off-label use. Ramosestron although belongs to a the class of serotonin 5-HT<sub>3</sub> receptor antagonist, has been found to be effective in all forms of nausea and vomiting but has not been approved by US-FDA for post-operative nausea and vomiting due to lack of safety data.

The use of buprenorphine and fentanyl for epidural anesthesia was observed in a large group of patients which is off label for its route of administration. Buprenorphine-approved dose is 300-450 µg for perioperative analgesia, but it was used in off-label manner at a lower dose, that is, 150 µg in all cases. This use may be justified by the physicians considering the lower body mass index in Indian individuals. The study also noted a higher occurrence of adverse events with increasing instances of off-label prescribing.<sup>7</sup>

### OFF LABEL PRESCRIBING IN PEDIATRICS

Off label prescribing in children is frequently observed as the number of drugs approved by the regulatory authorities in reference to pediatric indications is limited. Off label prescribing in preterm and full-term neonates, infants and in children younger than 2 years is even higher due to lack of sufficient clinical trial data. A trial conducted on pediatric general practitioners observed that off-label prescribing involved an unapproved indication in majority of prescription (56.4%) and age inappropriate dose in 45% prescriptions. The study further elaborated that the most commonly prescribed drugs were Nasal decongestants, first generation H<sub>1</sub> antihistamines and corticosteroids (betamethasone and prednisolone). Tixocortol is only approved for nasopharyngeal diseases with excessive mucus secretion in patients >15 years however it was commonly prescribed for allergic seasonal and vasomotor rhinitis. Prednisolone and betamethasone were prescribed with unlabeled indications for cough, bronchitis, or laryngitis.<sup>8</sup>

Use of corticosteroids in children for a prolonged duration is associated with disturbance in hypothalamic pituitary adrenal axis, subsequent growth retardation and development of Cushing's habitus. The long-term use of steroids must be therefore discouraged and should only be reserved for conditions that have authoritative approved indications.

A still higher incidence of off label prescribing was observed in hospitalized children. A study conducted on 243 hospitalized children in Gondar University Referral Hospital, Ethiopia indicated that 78.1% children were prescribed at least one off label medicine. The anti-microbial agents formed the highest used class of off-label pharmacological products (60.6%) followed by central nervous system drugs (14.3%) and Cardiovascular drugs (8.6%).<sup>9</sup>

A higher trend of off label use of anti-microbial agents is particularly seen in developing countries due to widespread incidence of infective diseases. However, start of anti-microbial agents in non-approved indications at an early

age leads to higher chances of anti-microbial resistance and therapeutic failure at a later stage of life.

The frequent anti-microbial off label prescribing is not limited to developing nations, neonatal prescribing pattern in a tertiary care hospital in Toronto revealed that the most commonly prescribed off label drug in neonates were anti-infectives like amoxicillin and gentamycin. The other anti infectives like acyclovir were also commonly prescribed. The most common reason cited for off label prescribing was for age followed by dosage in neonates.<sup>10</sup>

### OFF LABEL PRESCRIBING IN MEDICINE OUTPATIENT

A study conducted by nationally representative survey of physician in the United States reported that the overall prescription pattern indicated that out of total 725 million drugs prescribed by office-based physicians, 15% belonged to off label category. Off-label prescription was most common among cardiac medications (antianginals, antiarrhythmic, and anticoagulants), anticonvulsants and antiasthmatics. The off label prescribing was infrequent with anti-diabetic medications (<1%) and analgesics. A great disparity between labelled and off label prescribing was seen with psychiatric and neurological medications. Gabapentin had the highest proportion of off label use and only 20% of its off-label use had strong support compared with 80% with limited or no support. Conversely anti-hypertensive medications had highest degree of scientific supportive evidence. The study demonstrated a large variability in off label prescribing among different classes of drugs.<sup>11</sup>

### OFF LABEL PRESCRIBING IN DERMATOLOGY

Studies have indicated that the off-label prescribing was considerably higher in the earlier times. The study conducted by Sugarman et al noted that the off-label prescribing in a dermatology general hospital ranges from 17 to 73% with a weighted mean of 32%. The conditions most frequently managed with off-label prescriptions were acne rosacea (73%) and actinic keratosis (52%), whereas those with the fewest off label prescriptions were atopic dermatitis (17%) and psoriasis (16%).<sup>12</sup>

Picard et al. (2003) observed that only 14% of prescription drugs were off labeled. Inflammatory and hypersensitivity dermatoses were the most frequent indications of off-label prescriptions (26%). Treatments which most frequently corresponded to off-label prescriptions were topical corticosteroids and methotrexate.<sup>13</sup>

Another trial conducted by Danes et al (2012) observed a higher off label use of immunosuppressant products. The most frequent medicines were rituximab (21.1%), botulinum toxin (10.7%) and omalizumab (6.0%) and in most of the cases the level of evidence was quiet low.<sup>14</sup>

Diana Silva et al (2014) discussed Off-label prescribing for allergic diseases in children. They recognized that a high percentage of prescriptions performed for allergy treatment in daily clinical practice were off label. This can be explained by the lack of clinical research in pediatric age group caused

by mainly ethical and technical issues.<sup>15</sup>

Off label prescribing of topical steroids is widespread in India. A study conducted at a rural tertiary care hospital in India concluded that 28% of prescription had Topical steroids, out of which 98% were very potent corticosteroids; and in 85% of cases, the basis of prescribing these could not be established.<sup>16</sup>

Widespread use of topical steroids in off label manner is supported by the evidence that these medications are perceived to be safe by the prescribing physicians as they do not cause systemic steroid toxicity. However topical adverse effects of these medications are often ignored. Another evidence suggesting the use of topical steroids is the availability of these drugs in in fixed dose combinations(FDC's) with other agents. More than 119 FDCs of these corticosteroids with other agents (antibacterial, antifungal, keratolytic etc.) are available in the country, these preparations are misused by the physicians when clear diagnosis is not made.<sup>17</sup>

### OFF LABEL PRESCRIBING IN GYNECOLOGY

According to William F. Rayburn, et al. Off label drugs were prescribed mainly in the last months of pregnancy in order to avoid obstetric complications such as preterm delivery and eclampsia or to provide prophylactic care during delivery. A study conducted in Oklahoma, USA highlighted that most frequently prescribed off label drugs in pregnancy were broad spectrum antimicrobials to prevent neonatal sepsis. Another drug that was frequently prescribed was Betamethasone, in order to enhance fetal maturity. Notably both these group of drugs were prescribed in the last trimester of pregnancy. Terbutaline was prescribed in an off-label manner in order to inhibit premature labor in the second trimester. The study also highlighter the fact that on no occasion the patients were informed that the drug was recommended for an off-label indication.<sup>18</sup>

Another study conducted in a large group of patients in Liverpool, UK determined the safety of off label drugs in pregnancy. More than 17000 prescriptions with 235 different drugs were analyzed. 24% of the total off label drugs were generally classified as safe by the manufacturers, which mainly included drugs such as erythromycin, prochlorperazine and clotrimazole. Strikingly 58% of the off-label drugs prescribed were either contraindicated or cautioned by the manufacturers; another 16% of all the off-label drugs (eg: lisinopril, diazepam and morphine) belonged to the high-risk group. Therefore this study indicated that a large number of off label in pregnancy are associated with high risks, the prescribing physicians must be aware of the risk associated with these drugs.<sup>19</sup>

### CONCLUSION

Off label prescribing is termed as prescribing medicines for an indication that has not been approved by regulatory authorities. This off label prescribing practices are seen in all fields of medicine, however it is commonly seen in patient population who are less likely to be exposed in clinical trials (paediatric, gynaecology and geriatric population).

The prescribing of off label drugs should be encouraged as it leads to therapeutic exploration of the pharmaceutical product. However, this prescribing practice should be backed by strong scientific evidence to provide maximum benefit to the patient.

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