PharmacologyOnLine

Archives • 2021 • vol.2 • 138-144

FREQUENCY OF OFF-LABEL DRUG USE IN MEDICINE

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Abstract

Over the past 10-15 years, the use of drugs off-label (outside the label) has become common. Many authors of such publications believe that the practice of using drugs off-label has become so widespread that almost every drug is prescribed off-label. An analysis of the 10-year use of off-label drugs in the EU countries made it possible to estimate the frequency of such use, the number of leading drugs, the frequency of off-label use of original and generic drugs, depending on the frequency of their use for licensed indications and depending on their use in various areas of medicine. On average, off-label drugs were prescribed in 20% of cases, while in pediatrics, geriatrics, obstetrics and oncology, off-label drug prescription was more than 50%. At the same time, it is also worrying that almost three quarters of off-label prescriptions for drugs did not have convincing scientific support. Thus, the above data on the use of off-label drugs indicate: • an increase in the frequency of off-label drugs use; • about the widespread use of this type of therapy in such areas of medicine as pediatrics, oncology and psychiatry.

All of the above obliges to analyze and systematize both the positive experience of using off-label drugs and the negative consequences of such use, as well as present the results of the analysis of the frequency of use and the effectiveness of off label therapy to the medical community.

Key words: *pharmacotherapy, drugs, prescription off-label, different pharmacological groups.*

Over the past 10-15 years, the use of drugs off-label (outside the label) has become common. However, the prevalence of off-label prescribing, both in different countries and in certain areas of medicine, is difficult to assess, since there are no official statistics and reliable data on such use of drugs. Nevertheless, information published over the past 20 years indicates that the widespread use of off-label drugs in medicine occurs both in the EU countries and in other countries of the world [1-4].

Many authors of such publications believe that the practice of using drugs off-label has become so widespread that almost every drug is prescribed off-label [5]. In 2001, the American Academy of Medicine (AMA) analyzed off label drug use. The analysis showed that 73% of off-label drug use had no evidence of clinical efficacy and only less than one third (27%) of cases had strong scientific evidence [1].

A policy review published in 2005 reported that of 30 FDA studies conducted between 1985-2004, off-label drug use ranged from 11% to 80% and was used more frequently in younger patients than in the elderly. On average, off-label drugs were prescribed in 20% of cases, while in pediatrics, geriatrics, obstetrics and oncology, off-label drug prescription was more than 50%. A 2009 study showed that from 2001 to 2004, 62% of young children were prescribed prescription drugs off label for outpatient treatment [6].

In 2017, a US hospital study included patients who were prescribed at least one off-label drug for treatment. The results of the study showed that most often off-label drugs were prescribed for unapproved indications (74%). The number of off-label drug prescriptions increased with the deterioration of the patient's condition, and the main reason for this was the lack of an alternative for prescription. At the same time, it is also worrying that almost three quarters of off-label prescriptions for drugs did not have convincing scientific support [7].

In 2012, American pediatricians found that 96% of children from 13 to 17 years old were prescribed off-label treatment in intensive care units. More often, pediatricians, rather than family doctors, prescribed medicines for unlicensed indications (11.6% versus 3.6%, p <0.001). Depending on the age of the patient and the underlying disease in pediatrics, the use of off-label drugs varies from 30 to 90%, and the average practice of prescribing off-label drugs in pediatrics in the United States is approximately 50% of all prescribed drugs. An analysis of this problem in the United States showed that the use of off-label drugs for most drugs occurs 5 years after their appearance on the market, when almost 60% of drugs are prescribed by doctors for new indications. The top five most prescribed off-label drugs were cardiovascular (46%), anticonvulsant (46%), anti-asthmatic (42%), antiallergic (34%) and psychotropic (31%) drugs [8]. Off-label prescriptions with limited or no scientific support were most common among psychotropic (96%) and antiallergic (89%) drugs. Among generics and original medicines, generics are more often used off-label [8]. Off-label prescriptions with limited or no scientific support were most common among psychotropic (96%) and antiallergic (89%) drugs. Among generics and original drugs, generics are more often used off-label [9-11]. It turned out that most often (in 76% of cases) off-label drugs were prescribed to children from 1 to 2 years old, in second place were patients from 1 to 12 months. Using multivariate regression analysis, it was found that pediatric patients aged 0 to 2 years receive drugs off label more often than in any other age group [12]. Of these, antibacterial and anticonvulsant drugs were most often prescribed off-label. About 80% of neonates received at least one off-label drug [13].

In the USA, the prescription of drugs off-label was most common in newborns (83%) and this is associated with polypharmacy and chronic diseases [14-16]. The relative and absolute rates of off-label prescriptions in recent years have increased for antihistamines and some psychotropic drugs, while off label antibiotic prescriptions have been stable or declining. The results of this study are consistent with the downward trend in antibiotic prescriptions over the past 20 years, especially for penicillins and cephalosporins [17, 18].

Thus, an analysis of the use of off-label drugs in the United States showed that their prescription increased over time for many pharmacological groups of drugs, especially for antihistamines, antidepressants, antiepileptic, antiadrenergic drugs, corticosteroids, NSAIDs. Among antibacterial drugs, the most commonly prescribed off-label are penicillins, macrolides, clindamycine and

cephalosporins; among antidepressants - sertraline (93%) and fluoxetine (37%); among NSAIDs - ibuprofen (5%) and diclofenac sodium (95%) [8].

An analysis of the 10-year use of off-label drugs in the EU countries made it possible to estimate the frequency of such use, the number of leading drugs, the frequency of off-label use of original and generic drugs, depending on the frequency of their use for licensed indications and depending on their use in various areas of medicine [19].

As this analysis shows, off-label drugs are most often used in pediatrics and neonatology. According to the European Scientific Center for Children's Health, more than 45% of drugs used in children's hospitals and 80-90% for outpatient prescriptions are used off label. The likelihood of using drugs off-label is higher in young children and patients with rare diseases, especially in the neonatal period, when almost all drugs (up to 90%) are prescribed off-label. The prevalence of unlicensed use of various drugs in newborns in developed European countries ranges from 36-93% [20-22]. The results of many retrospective studies have shown that, on average, in European countries, from 10 to 67% of children received off-label drugs [20, 23]. Thus, the prescription of drugs off-label in pediatric practice was: up to 11% - in the UK, 33% - in France, 29% - in the Netherlands [23-25]. Systemic antibiotics, analgesics, and bronchodilators are the most commonly used off-label drugs in dermatological and ophthalmic pediatric practice [18]. Pharmacists in the UK currently automatically replace prescribed off label drugs, unless the doctor specifies that off label drugs should not be replaced, so the frequency of off-label drug prescriptions is on the rise [26]. Analysis of literature sources indicates that paracetamol, salbutamol, inhaled corticosteroids, cefotaxime, amoxicillin, caffeine, prednisolone, morphine and heparin are often prescribed in off-label pediatric practice. This is because three quarters of the medicines used in pediatrics are not licensed for use in children. Inappropriate dosage of antibiotics is the most common reason for off-label use in the UK, Germany and Italy [18, 26, 27]. In Germany, the national child and adolescent health survey provided data on off-label drug use in this population. Analysis of the use of prescription drugs showed that 20% of prescribed drugs are used off-label [27-29].

In 2009, scientists at the Institute of Pediatrics in Australia found that 62% of children's outpatient visits to doctors ended with the prescription of drugs off-label [30]. Also, an analysis of off-label drug use in Australia showed that 80% of children in neonatal intensive care units received drugs that did not pass the approval process for this patient category. Most often (67.2%) use off-label drugs that affect the cardiovascular system, least of all - drugs for the treatment of the genitourinary system and sex hormones (13.3%). At the age of 2 years, the most frequently used off-label drugs were drugs for the sensory organs, then for the treatment of the respiratory system and antimicrobial agents for systemic use. Between the ages of 3 and 10, off label drugs were most commonly used to treat the gastrointestinal tract. In adolescents and older (from 11 to 17 years old), off label drugs are also often used. These are drugs that affect the digestive tract and metabolic processes, as well as dermatological and affect sensory organs [31].

In India, off-label antibiotics and anticonvulsants are most commonly used in children. Dose and age were found to be the most common causes of drug off label use. Thus, in 2011, out of 320 patients included in the study, 310 (97%) received at least one off-label drug. Of the 1645 drugs used during hospitalization, 1152 (70%) were assigned off-label. The most common reason for prescribing an off-label 893 (63%) drug was a higher dose of use than that indicated for specific pediatric patients [32].

In 2010, a retrospective analysis of the use of off-label drugs in 3 children's departments of one of the largest pediatric nephrology centers in China showed that the use of off label drugs was 98, 78.96 and 88.05%, respectively [33]. The situation was similar in the Central Children's Hospital of Italy: up to 30% of all drugs were used off-label, and in general, 42% of children received medical care in violation of the recommendations specified in the drug instructions [33, 34].

In Russia, doctors also often prescribe off-label drugs based on information obtained from journals, brochures, television and from colleagues who are not responsible for recommendations. To identify the prescription of drugs off-label to children with violation of the instructions in Russia, the data for the period from 2009 to 2011 were studied by the method of retrospective analysis.

A total of 2375 reports on the development of PR in children who received off- label drugs were analyzed for the specified time interval. The majority (41%) of reports were about the use of drugs that are not approved for use in childhood. There were 398 cases of their use with violations of the instructions for medical use. For example, in 20.6% of cases, a dose was found in the prescriptions that was different from that indicated in the instructions; in 20.6% of cases - an unreasonable route of drug administration; 17.3% - unregistered readings [35, 36].

Integrated results of pharmacoepidemiological study in Russia show that there is a tendency to increase the use of off-label antimicrobial drugs for systemic use (42.6%), drug overdose (36.2%), violation of age restrictions (32%), use for unlicensed indications (19 ,one%). In general, 2/3 of the drugs used to treat children in Russia have not been studied in clinical trials in this population and therefore are not officially approved for use in pediatric practice. Consequently, the analysis of the prescription of drugs in pediatric practice in Russia shows that their use off label is a large-scale phenomenon, both in hospital and in outpatient treatment [36]. The vast majority of children, including newborns, can be prescribed at least one off-label drug in hospital treatment. At the same time, the appointment of off-label cardiovascular drugs ranged from 55.2 to 56.4%, anti-inflammatory drugs - from 45 to 46%, antidepressants - from 36.6 to 40.4%, antiepileptic drugs - from 14.2 to 15%, and antipsychotic drugs - from 7.8 to 13.2%. Antibiotics (75%) and inhaled corticosteroids (79%) were prescribed off-label, mostly at higher doses than those recommended. For diseases of the respiratory system, many drugs (39.5%) were prescribed below the age limit specified in the instructions [36].

Thus, various regional and international studies indicate that off-label prescription of drugs ranges from 18 to 60% in young children and up to 90% in newborns. There is data on the frequency of off-label drug use of different pharmacological groups. So, blood products are used with violations of instructions in 89% of cases, affecting the metabolism - 86%, the respiratory system - 82%, hormonal drugs - 80%, antibacterial agents for systemic use - 73%, drugs for the treatment of the cardiovascular system - 71%, gastrointestinal tract and nervous system - 53%. The least commonly used off-label antiparasitic drugs (16%) [37].

Among drugs that affect the nervous system, off-label use is most common in the group of anticonvulsants and antidepressants, while the results of a 2006 study showed that in 73% of cases the prescription of off-label drugs did not have convincing scientific evidence [8]. In 2012, in adults, drugs were most often used off- label for the treatment of CNS diseases (26.3%), among which anticonvulsants (66.6%), antipsychotic (43.8%) and antidepressants (33.4%) were in the lead. A more recent study (2016) found the frequent prescription of off-label anticonvulsants (74%) and antipsychotic (60%) drugs. Of the psychotropic drugs, the most commonly used off-label were gabapentine (83%), amitriptyline (81%), clonazepam (12.4%), lorazepam (12%) and trihexiphenydil (10%) [8].

Consequently, the scope of off-label prescriptions varies widely, exceeding 50% for certain drugs and pharmacotherapeutic groups. In addition to the generally accepted trends in the use of off-label drugs described above, data on the regional characteristics of their off-label prescription have been published. So, in India, antimicrobial drugs (ceftriaxone, amikacin), drugs for systemic use in diseases of the blood, gastrointestinal tract, metabolism, salbutamol, lorazepam and ondansetron are more often prescribed off-label in doses and by age categories that differ from those indicated in instructions. In Italy budesonide was the most commonly used off-label drug (80%), in the Netherlands salbutamol (32.8%), in the UK beclomethasone (25.8%) [35].

An analysis of the problem of the frequency of off-label drug use suggests that this therapy is more typical for pediatrics, psychiatry and oncology. So, in Russia, the largest number of cases of the use of drugs not approved for use in pediatrics was observed in the group of antimicrobial (19%), psychotropic (16%), antiviral (4.9%), enzymatic (4.9%) drugs, alpha-adrenomimetics (4.3%) and NSAIDs (3.7% [9]. Of the group of antimicrobial drugs, furazolidone was most often prescribed in violation of the age limit for the treatment of intestinal infections. According to the instructions, this drug is contraindicated in children under one year of age, but it was prescribed to children aged 3 to 10

months. As a result, all patients developed toxicoderma, which led to hospitalization and long-term treatment. The choice of the drug was inappropriate, since there are enough drugs on the pharmaceutical market for the treatment of these nosologies that are approved for use in small children.

In an analysis of 1,017 prescriptions for 293 pediatric patients, the most commonly used drugs were paracetamol (14%), cefotaxime (8%), amoxicillin (7%), caffeine (4%), and prednisolone (4%). Of these, in 443 cases the drugs were used off - label, and in 285 (28%) they were not approved for use in children. [14].

Such a frequency of off-label drugs use in the treatment of children may be due to the fact that pediatricians do not have a sufficient arsenal of drugs approved for use in pediatrics. Clinical trials in children are resource intensive and require specific legal and ethical considerations. This is the reason for such a small number of licensed drugs for which there is reliable information on the safety of their use in children. Another reason is that for many drugs there are no medicinal forms convenient for use in pediatric practice.

Psychiatry is the second area of medicine after pediatrics where off-label drugs are widely used. According to published data, one-fifth of all psychotropic drugs are prescribed off-label. The use of such off-label drugs in the United States increased from 84% in 1995 to 93% in 2008. Today, this pharmacological group in the United States is still one of the most prescribed, including off-label. About 10% of Americans take off label antidepressants, especially women in their 40s and 50s. The widespread off-label use of these drugs in the UK is a matter of serious concern, especially since only 4% of the use is scientifically substantiated. The most frequently used off-label were anticonvulsants (74%) and antipsychotic drugs (60%) [10]. Atypical antipsychotics and antidepressants have been used especially often without convincing evidence when there are statistically significant risks associated with these drug groups, including death, cardiovascular disorders, movement disorders, fatigue, severe sedation and weight.

In oncology, the frequency of off-label drugs is more than 50%. Thus, according to available information in the United States, about half of anticancer drugs are prescribed off-label [38]. Analysis of more than 5,000 prescribed antiblastomic drugs revealed that one third of them were used off-label, more than 50% of patients received at least one drug off-label. The degree of off-label drug use varied according to the type and stage of cancer. In general, the use of off-label drugs was higher in patients with advanced cancer. The reason for the widespread use of off-label drugs for the treatment of malignant tumors is the large number of their types and the sensitivity of the same type of tumors (for example, glandular tissue) to other drugs (for example, trastazumab). Therefore, one anticancer drug can be used in the treatment of several types of tumors. However, many well-known anticancer drugs do not contain in the instructions all the indications for which they can be effectively used. Depending on the stage of the tumor, one or more drugs can be used off-label. This is confirmed by the results of a survey of specialists from the National Global Network of Cancer Centers in the USA, conducted in 2005, which revealed that 50–75% of all drugs in oncology are used off label, especially for generic drugs [38]. It should be noted that the use of off label drugs in oncology concerns not only anticancer drugs, but also drugs of other pharmacological groups. For example, tricyclic antidepressants are used in oncology to treat neuropathic pain in cancer patients. In addition, there are many reports of off-label use of SSRI drugs [37].

Thus, the above data on the use of off-label drugs indicate:

- an increase in the frequency of off-label drugs use;
- about the widespread use of this type of therapy in such areas of medicine as pediatrics, oncology and psychiatry.

All of the above obliges to analyze and systematize both the positive experience of using off-label drugs and the negative consequences of such use, as well as present the results of the analysis of the frequency of use and the effectiveness of off label therapy to the medical community.

References

1. Bennett W. M. Of-label use of approved drugs: therapeutic opportunity and challenges // J. Am. Soc. Nephrol. – 2004. – Vol. 15. – P. 830–831.
2. Christine Allen H., Connor Garbe M., Lees Julie, Aziz Naila et al. Off-label Medication Use in Children, More Common Than We Think: A Systematic Review of the Literature // J. Okla State Med. Assoc. – 2018. – Vol. 111 (Iss. 8). – P. 776–783.
3. Conti R. M., Bernstein A. C., Villaflor V. M. et al. Prevalence of off-label use and spending in 2010 among patent-protected chemotherapies in a population-based cohort of medical oncologists // J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. – 2013. – Vol. 31, N 9. – P. 1134–1139.
4. Graziul C., Gibbons R., Alexander G. C. Association between the commercial characteristics of psychotropic drugs and their off-label use // Med. Care. – 2012. – Vol. 50, N 11. – P. 940–947.
5. Ditsch N., Kumper C., Summerer-Moustaki M. et al. Off-label use in Germany – A current appraisal of gynaecologic university departments // Eur. J. Med. Res. – 2011. – Vol. 16, N 1. – P. 7–12.
6. Palmaro A., Bissuel R., Renaud N. et al. Off-label prescribing in pediatric outpatients // Pediatrics. – 2015. – Vol. 135, N 1. – P. 49–58.
7. Brown Gregory P., Stewart L. A., Rabinowitz T. et al. Approved and offlabel use of prescribed psychotropic medications among Federal Canadian Inmates // The Canadian J. of Psychiatry. – 2018. – Vol. 63 (Iss. 10). – P. 683–691.
8. Sohn M., Moga D. C., Blumenschein K., Talbert J. National trends in off-label use of atypical antipsychotics in children and adolescents in the United States // Med. (United States). – 2016. – Vol. 95 (Issue 23). – P. e3784. doi: 10.1097/MD.0000000000003784
9. Tabarrok A. T. Assessing the FDA via the anomaly of off label drug // Independant Review. – 2000. – Vol. 5 (Iss. 1). – P. 25–53.
10. Vijay A., Becker J. E., Ross J. S. Patterns and Predictors of Off-label Prescription of Psychiatric Drugs // PLoS One. – 2018. – Vol. 13 (Iss. 7). – P. 1–13.
11. Zen L. De, Marchetti F., Barbi E. et al. Off-label Drugs Use in Pediatric Palliative Care // Italian J. of Pediatrics. – 2018. – Vol. 44 (Iss. 1). – P. 1–6.
12. Kumar P., Walker J. K., Hurt K. M. et al. Medication use in the neonatal intensive care unit: current patterns and off label use of parenteral medications // J. Pediatr. – 2008. – Vol. 152. – P. 412–415.
13. HalineTereza Matias de Lima Costa, Tatiana Xavier Costa, Rand Randall Martinset al. Use of Off-Label and Unlicensed Medicines in Neonatal Intensive Care // PLoS One. – 2018. – Vol. 13 (Iss. 9). – P. 1–12.
14. Pandolfini C., Bonati M. A literature review on off-label drug use in children // Eur. J. Pediatr. – 2005. – Vol. 164, N 9. – P. 552–558.
15. Cuzzolin L., Atzei A., Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: A review of the literature and a consideration about drug safety // Expert Opin. Drug. Saf. – 2006. – Vol. 5, N 5. – P. 703–718.
16. Cuzzolin L., Atzei A., Fanos V. Unlicensed and off label uses of drugs in paediatrics: a review of the literature // Fundam. Clin. Pharmacol. – 2003. – Vol. 17. – P. 125–131.
17. Chua K. P., Fischer M. A., Linder J. A. Appropriateness of outpatient antibiotic prescribing among privately insured US patients: ICD-10-CM based cross sectional study // BMJ. – 2019. – Vol. 16. – P. 364: k5092. doi: 10.1136/bmj.k5092.
18. Maria A., Dr. Somia Gul. An Emergence of a MRAB. With Growing Necessity of Antibiotic Pharmacist in Infectious Era // Pharm. Ann. Acta. – 2016. – Vol. 7, N 6. – P. 491–504.152.
19. Edwards I. R. Off label pharmacovigilance // Drug. Safety. – 2011. – Vol. 34, N 10. – P. 795–797.
20. Conroy S., Impicciatore P., Knoeppel C. et al. Survey of unlicensed and off label drug use in pediatric wards in European countries. European Network for Drug Investigation in Children // BMJ. – 2000. – Vol. 320 (Iss. 7227). – P. 79–82.
21. Lass J., Irs A., Pisarev H. et al. Off label use of prescription medicines in children in outpatient setting in Estonia is common // Pharmacoepidemiol. Drug. Saf. – 2011. – Vol. 20, N 5. – P. 474–481.
22. Laughon M. M., Capparelli E. V., Kearns L. G. et al. Innovative clinical trial design for pediatric

therapeutics // Expert. Rev.Clin. Pharmacol. – 2011. – Vol. 4. – P. 643–652.
23. Drogou François, Netboute A., Giai J. et al. Off-label Drug Prescriptions in French General Practice: A Cross-Sectional Study // BMJ Open. – 2019. – Vol. 9 (Iss. 4). – P. 1–8.
24. Emmerich J., Dumarcet N., Lorence A. France's new framework for regulating off label drug use // N. Engl. J. Med. – 2012. – Vol. 367, N 14. – P. 1279–1281.
25. Jong G. W., Bakker E. M., Stricker B. H. C. et al. Unlicensed and offlabel drug use in a pediatric ward of a general hospital in the Netherlands // Eur. J. Clin. Pharmacol. – 2002. – Vol. 58. – P. 293–297.
26. Aronson J. K., Ferner R. E. Unlicensed and off label uses of medicines: definitions and clarification of terminology // Br. J. Clin. Pharmacol. – 2017. – Vol. 83 (Iss. 12). – P. 2615–2625.141.
27. Sturkenboom M., Felisi M., Manfredi C. et al. Pediatric status and off label use of drugs in children in Italy, United Kingdom and the Netherlands // Pharmaceut. Policy Law. – 2009. – Vol. 11. – P. 51–59.
28. Knopf H., Wolf I.-K., Sarganas G. et al. Off-label medicine use in children and adolescents: Results of a population-based study in Germany // BMC Public. Health. – 2013. – Vol. 13, N 1. – P. 1–11.
29. Mukattash T. L., Millership J. S., Collier P. S. et al. Public awareness and views on unlicensed use of medicines in children // Br. J. Clin. Pharmacol. – 2008. – Vol. 66, N 6. – P. 838–845.
30. Mulligan E., Messenger H. Mifepristone in South Australia – the first 1343 tablets // Aust. Fam. Physician. – 2011. – Vol. 40. – P. 342–345.
31. Ballard C. D., Paterson G. M., Thompson A. J. et al. Off-label use of medicines in pediatric inpatients at an Australian teaching hospital // J. Paediatr. Child. Health. – 2012. – Vol. 49. – P. 38–42.
32. Levêque D. Off label use of anticancer drugs // Lancet.Oncol. – 2008. – Vol. 9 (Iss. 11). – P. 1102–1107.
33. Liu L. Hong-Yu Yang, Yan Lou et al. Off-label prescriptions in intensive care unit: the Chinese experience // Therapeutics and Clin. Risk Management. – 2018. – Vol. 14. – P. 195–202.
34. Bajcetic M., Jelisavcic M., Mitrovic J. et al. Off-label and unlicensed drugs use in pediatric cardiology // Eur. J. Clin. Pharmacol. – 2005. – Vol. 61. – P. 775–779.
35. Volskaya E. New perspectives for children's medicines // Remedium. - 2007. - № 8. - P. 1–6.
36. Causes and legal aspects of the off label drugs emergence: literature review / Kalko K. O., Drogovoz S. M., Komarova A. P., Hailat I. A., Drogovoz K. V., Ivantsyk L. B. Pharmacologyonline. Vol. 3. 2021. P. 179-186. https://pharmacologyonline.silae.it/files/archives/2021/vol1/PhOL_2021_1_A024_Kalko.pdf
37. Off label use - medicines without instructions - monograph / Drogovoz S. M - Kharkiv: Title, 2021. - 301 p.
38. Poole S. G., Dooley M. J. Off-label prescribing in oncology // Support Care Cancer. – 2004. – Vol. 12 (Iss. 5). – P. 302–305.