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A review of pharmacoepidemiology research in the mental health field

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Abstract

Pharmacotherapy for patients with mental illnesses needs to be founded on research. Pharmacoepidemiology has been made more accessible by the availability of digital data, which allows observational studies to be conducted on real-world medications' efficacy. Pharmacoepidemiology allows understudied groups to be studied in their natural settings because of large patient samples. As well as being more cost-effective and quicker to conduct than randomized controlled trials, this research may focus on long-term effects, generic medicines, and discontinuing medication (deprescribing). We can contribute to developing already-marketed medicines by combining pharmacoepidemiology and pharmacovigilance techniques. In observational pharmacoepidemiological studies, treatment selection is not randomized, resulting in confounding by indication. Potential solutions to this problem include active comparative groups, within-individual studies, and propensity scoring. Triangulation of multiple analytical approaches has strengthened many more rigorous pharmacoepidemiology studies and enhanced Belief in the Relationships inferred from causality. As data resources and analytic methods advance, guidelines must incorporate evidence from randomized controlled trials and observational pharmacoepidemiological studies. By cooperating with guideline writers, pharmacoepidemiology researchers can provide answers to essential policymaker queries and ensure that their conclusions are incorporated into the evidence base. To take full advantage of upcoming opportunities, statistical and data science techniques must be advanced, outreach and engagement must be increased, and capacity building (data resources and researcher base).

Keywords: *Pharmacoepidemiology, mental health, pharmacovigilance*

INTRODUCTION

In the past, pharmacoepidemiology was described as the study of the consumption of drugs and their effects on a Population of a large size.[1] Pharmacoepidemiological There are a variety of studies, from those that describe prescribing patterns to those that are quasi-experimental to those that are large; our research is based on observational methods based on cohort and case-control studies. [2-4] Additionally, the validity of the findings has been enhanced by employing specialized statistical methods. It discusses how pharmacoepidemiology can contribute to the field regarding its advancements and challenges. As medication decisions for people with mental health needs become more complicated, observational forms of pharmacoepidemiology are becoming increasingly important. Sometimes, randomized controlled trials (RCTs) are believed to be the only way to examine medication safety, which is unfortunate for observational pharmacoepidemiology studies. [5-7]

Observational studies occasionally have benefits over RCTs, even though RCTs give us solid indicative evidence of efficacy. Several new study designs have contributed to the sophistication of observational pharmacoepidemiology, addressing confounding issues that would otherwise limit the utility of observational studies. We assert that

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pharmacoepidemiology, like large-scale compared efficacy and pharmacovigilance studies, can be used more effectively to design an evidence-based approach.

Pharmacoepidemiology's benefits:

Randomized controlled trials (RCTs) are widely recognized as the standard method for evaluating the efficacy of clinical therapies. This is primarily due to the random assignment of participants to treatment groups and the rigorous control of experimental conditions.[7]

Yet, real-world data can also be used to address the drawbacks of RCTs.

Sample size:

Trials testing psychiatric treatments can have difficulties recruiting and retaining participants. In the BALANCE RCT[8], patients with bipolar affective disorder type 1 were randomly assigned to either valproate or lithium treatment (or a combination of both). Although the study had intended to recruit 3000 participants[9], 330 participants were recruited across 41 sites over six years, of whom 167 completed the 2-year protocol.[8] Comparatively, Hayes et al.[10] reviewed outcomes across 5089 bipolar disorder patients treated with lithium, valproate, olanzapine, or quetiapine using primary care databases over up to 17 years. It was reported that clinical inclination changed towards second-generation antipsychotics when the CUtLASS-1 trial[11] of second-generation antipsychotics was blocked in recruitment. This observation demonstrates[11] that randomized controlled trials (RCTs) often require a significant amount of time to conduct, leading doctors to hesitate to enroll patients in trials that may potentially assign them to older antipsychotic medications through randomization. An analysis designed retrospectively can mitigate this problem.

Population:

To advance the field of personalized medicine, it is imperative to establish empirical evidence supporting the efficacy of specific treatments within particular subpopulations. Nevertheless, the criteria for inclusion and exclusion in clinical trials are typically restrictive. The requirement of permission in some form is necessary for participation in the study due to the potential risks and burdens imposed on the subject. However, the competence to consent to mental disorders may occasionally be impaired. Patients suffering from learning disorders and schizophrenia patients are rarely studied in trials.[12] To enhance the involvement of marginalized groups in research, it is imperative to implement more efficient research methods and laws. Additionally, using alternative trial approaches will play a significant role in broadening the existing body of data.[12,13] The utilization of routine data derived from anonymous registries, including certain national databases that possess widespread accessibility, in conjunction with pharmacoepidemiology methodologies, yields findings that possess broad applicability to the general population and specific subgroups while minimizing the potential for adverse consequences and discriminatory practices.

Outcome selection:

The efficacy and safety of medicines must be determined over a long period since many mental health conditions first manifest in adolescence and continue over time. Integrating electronic health record research databases with additional administrative datasets can yield optimal insights into real-world results. Psychiatric records combined with healthcare utilization data demonstrate that antipsychotic treatment confers a protective effect on mental health[14,15] and that maintenance therapy during pregnancy reduces maternal mental illness.[16] A wide variety of long-term consequences of public health significance will now be captured by combining education, employment, crime, and census records. Through establishing links to employment, education, criminal records, and census data, research has the potential to capture broader long-term outcomes, which are crucial for public health.[17,18,19] As a result, when the secondary use of data is aimed at assessing treatment response, conventional scales may be unable to do so.[20]

Rare outcomes:

When evaluating the safety of drugs, it is possible to assess the risk of uncommon events by utilizing a large amount of real-world data.[21] To maintain comprehensive healthcare data surveillance, medicine regulators increasingly use pharmacovigilance.[22] Pharmacoepidemiology is used to conduct safety analyses[23] on SSRIs' effects on fetal abnormalities and clozapine's mortality effects.[15] Analyzing large databases of adverse events could help pharmacovigilance efforts Assessment of the possibility of safety of newly formulated medications.[24] The rarity of the side effects caused by drug-drug interactions makes them challenging to detect in RCTs and co-prescribing drugs is frequently restricted. Using a database study, Malik et al.[25] confirmed the hypothesis that sodium valproate co-prescribing is associated with an increased risk of neutropenia with clozapine. To ascertain intricate adverse effects, such as the impact of anticholinergic drugs on delirium[26] or asthma medications on suicide, it is imperative to utilize extensive observational datasets.[27]

Funding and untypical treatments:

Utilizing RCTs to test pharmacological treatments can be very costly[28]. The evidence base may inadvertently favor new therapies due to the disparity in funding between old and new medications. As is well known, clinical trial reporting is also affected by conflicts of interest.[29,30] Pharmaceutical companies rarely fund observational pharmacoepidemiological studies since they tend to cost less than randomized controlled trials (RCTs). Due to this imbalance in evidence, studies of this kind might help to rectify it. Studying pharmacoepidemiology through observational methods allows for the identification of drugs prescribed for a different purpose but could be repurposed for treating mental disorders. In a study conducted by Hayes et al., it was observed that patients diagnosed with severe mental illness, as recorded in the Swedish national database, exhibited a reduced likelihood of mental health-related

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hospitalizations when they were prescribed statins for cardiovascular health, in comparison to those who did not receive statin treatment. While hospitalization was not found to be connected with other cardiovascular medicines, the study recognized statins as potential therapeutic options for managing severe mental illness. Pharmacoepidemiological approaches, such as examining antipsychotic polypharmacy, can be employed to investigate the prevalence of prescribing practices that deviate from established recommendations.[31]

RCTs are unable to answer specific questions:

One obstacle to the key to using antidepressants effectively is knowing which one will work best for each patient. Approximately 37% of patients who try an antidepressant for the first time respond, but 67% respond after trying four or more antidepressant strategies (including augmentation and substitution).[32] RCTs have been unable to offer a generalizable approach for the first antidepressant prescription and subsequent prescriptions.[33] Observational pharmacoepidemiology, however, may be able to collect larger and more representative samples and provide richer data for these models to use, in addition to improving understanding of clinical efficacy predictors. Second, we need to know which antidepressants are safe for whom. According to RCTs mostly conducted on adults, SSRIs were formerly prescribed for use by young people due to their safety. This study's findings demonstrate an age-specific interaction between selective serotonin reuptake inhibitors (SSRIs) and self-harm tendencies within vulnerable subpopulations. Specifically, it suggests that individuals in their youth are particularly sensitive to engaging in self-harm behaviors and experiencing suicidal ideation when using SSRIs.[34] The analysis of Medicaid data in the United States also indicates a potential association between prolonged use of selective serotonin reuptake inhibitors (SSRIs) among young individuals and the manifestation of physical health complications, including type 2 diabetes.[40] In comparison to daily oral administration, long-acting injectable (LAI) antipsychotics are often regarded as providing superior efficacy as compared to oral antipsychotics, mostly because of enhanced patient compliance.[35] In a large RCT and subsequent meta-analysis, LAI was not found to prevent relapse in schizophrenia patients better than oral antipsychotics.[36,37] Compared to oral antipsychotics, LAIs were more effective at preventing hospitalizations, according to a study.[37] Pharmacoepidemiological studies must recognize the Constraints of observational research. In pharmacoepidemiology based on observational research [38], bias is more likely to arise from certain sources: Divergent group surveillance, inequitable observation periods, and confusion based on indications. Several guidelines exist to reduce bias in studies, including the choice of treatment and comparative groups, the start date, and the outcome.[2,3,39] It can increase confidence in findings when multiple secondary analyses are triangulated.[40]

Confounding:

The issue of confounding by indication or severity is a significant challenge in observational studies examining the effectiveness of different therapies.[5] Rather than randomly prescribing remedies, medical or psychiatric disorders are assessed according to severity and presence. An uncorrected analysis may lead to a conflation of treatment success with the presence and severity of the disease. As an example, if clozapine users were compared to those not on antipsychotics from a primary care registry, clozapine users would likely be the only ones with psychotic disorders; therefore, clozapine treatment and psychotic illness are confounded if the result is time for psychiatric admission. Clozapine is only used to treat psychosis that resists treatment, so comparing clozapine with first-generation antipsychotics would be unfair.[35]

The selection process for similar treatments may not be arbitrary, as it may also consider the profiles of their respective side effects. Based on an analysis of a primary care database, a comparative study examined the effects of quetiapine, risperidone, and olanzapine. The findings indicated that individuals initially administered olanzapine exhibited a comparatively lower body weight at the beginning of the study, in contrast to the other groups.[41] Individuals with elevated body weights tend to tend to avoid the usage of olanzapine. When designing and analyzing pharmacoepidemiological investigations, it is imperative to consider this issue.

Techniques for causal inference:

Scientific research is primarily concerned with inferring causality. The propensity score can address ambiguity by predicting the likelihood of a specific patient receiving the treatment of interest (e.g., treatment A rather than treatment B) based on the characteristics of the patient and the clinical environment.[42] According to an unadjusted analysis, olanzapine and risperidone were associated with lower cardiac events than second-generation antipsychotics. We used variables such as baseline weight and diabetes to create a score for the likelihood of receiving olanzapine. It was not evident that there was a significant difference in the risk of cardiovascular events between patients taking olanzapine and risperidone based on their likelihood scores.[43] Machine learning techniques can generate a propensity score with multiple variables by leveraging e-health records or other data sources that contain rich information. Simplistic models have the potential to yield comparable effectiveness to expert-based propensity ratings.[44] As an additional measure of bias and confounding, studies may include a "negative control," defined as an unknown exposure to the given outcome.[45] Designing within-individual studies also addresses confounding by indication.[39,46] Several studies have used this approach in treating severe mental illness with LAI antipsychotics[37] and repurposed agents.[47] The issue of comparable groups for patients receiving clozapine has also been examined using within-individual designs in our discussion. Based on the findings of a particular investigation, the utilization of clozapine for two years was linked with a mean reduction of 0.71 admissions (equivalent to 10 bed days) compared to the two years preceding the commencement of the study.[48]

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Conclusion:

The discipline of pharmacoepidemiology is experiencing significant growth in an era characterized by the widespread digitization of information. Studies conducted within the realm of pharmacoepidemiology offer valuable insights into a wide range of practical clinical challenges about individuals with mental health conditions. Hence, the cost-effectiveness of these studies holds significance in mental health research, given the hard funding landscape when juxtaposed with conventional clinical trial designs.[49] Pharmacoepidemiological research, however, has limited data; creating methods to overcome biases and confusion is also crucial. It is also necessary for decision-makers to actively involve themselves in evidence if high-quality studies are to have an impact on clinical practice. For pharmacoepidemiology to be effective, two groups must be raised in awareness: The academic and clinical communities must be able to produce more evidence based on actual needs. Secondly, the clinical and policy community should be prepared to assess and incorporate new findings into practice. (Fig.1)

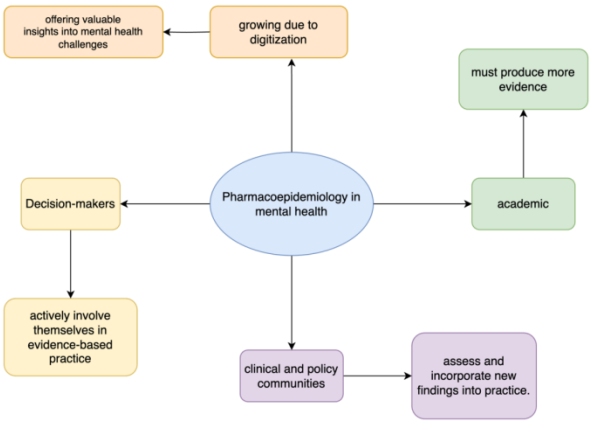

Figure1. Pharmacoepidemiology in mental health roadmap

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References

1. International Society for Pharmacoepidemiology. About pharmacoepidemiology. 2019. https://www.pharmacoepi.org/about-ispe/about-pharmacoepidemiology/ (accessed May 31, 2019).
2. European Medicines Agency. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guide on methodological standards in pharmacoepidemiology (revision 7). http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideonMethStandardsinPE_Rev7.pdf (accessed Oct 12, 2019).
3. Strom BL. Basic principles of clinical epidemiology relevant to pharmacoepidemiologic studies. In: Strom BL, Kimmel SE, Hennessy S, eds. Pharmacoepidemiology 5th edn. Oxford: John Wiley & Sons, 2012: 38-50.
4. Safer DJ, Zito JM. Pharmacoepidemiology of psychotropic medications in youth. In: Rosenberg DR, Gershon S, eds. Pharmacotherapy of child and adolescent psychiatric disorders 3rd edn. Oxford: John Wiley & Sons, 2012: 7-23.
5. Cole GD, Francis DP. Trials are best, ignore the rest: safety and efficacy of digoxin. *BMJ* 2015; **351:** h4662.
6. Bell H, Wailoo A, Hernandez M, et al. The use of real-world data for the estimation of treatment effects in NICE decision-making. NICE DSU technical support document. 2016. http://nicedsu.org.uk/methods-development/real-world-data/ (accessed Oct 12, 2019).
7. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the gold standard—lessons from the history of RCTs. *N Engl J Med* 2016; **374:** 2175–81.
8. The BALANCE investigators and collaborators. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 2010; **375:** 385–95.
9. Geddes JR, Rendell JM, Goodwin GM. BALANCE: a large simple trial of maintenance treatment for bipolar disorder. *World Psychiatry* 2002; **1:** 48–51.
10. Hayes JF, Marston L, Walters K, Geddes JR, King M, Osborn DP. Lithium vs valproate vs olanzapine vs quetiapine as maintenance monotherapy for bipolar disorder: a population-based UK cohort study using electronic health records. *World Psychiatry* 2016; **15:** 53–58.
11. Jones PB, Barnes TR, Davies L, et al. Randomized controlled trial of the effect on quality of life of second-*vs* first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry* 2006; **63:** 1079–87.
12. Shepherd V. Research involving adults lacking capacity to consent: the impact of research regulation on 'evidence biased' medicine. *BMC Med Ethics* 2016; **17:** 55.
13. Dunn LB, Jeste DV. Enhancing informed consent for research and treatment. *Neuropsychopharmacology* 2001; **24:** 595–607.
14. Mace S, Dzahini O, Cornelius V, Anthony D, Stewart R, Taylor D. Antipsychotic use and unexpected death: a hospital-based case-control study. *Acta Psychiatr Scand* 2015; **132:** 479–88.

*Corresponding Author: **Mohammad Hossein Hooshangi**

15. Cho J, Hayes RD, Jewell A, et al. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. *Acta Psychiatr Scand* 2019; **139:** 237–47.
16. Taylor CL, Stewart RJ, Howard LM. Relapse in the first three months postpartum in women with history of serious mental illness. *Schizophr Res* 2019; **204:** 46–54.
17. Perera G, Broadbent M, Callard F, et al. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. *BMJ Open* 2016; **6:** e008721.
18. Downs J, Gilbert R, Hayes RD, Hotopf M, Ford T. Linking health and education data to plan and evaluate services for children. *Arch Dis Child* 2017; **102:** 599–602.
19. Wood S, Rees S, Wang T, Marchant A, Akbari A, John A. Child health clinical outcome review programme: the mental healthcare of young people and young adults. *Int J Popul Data Sci* 2018; **3**.
20. Clark DM, Canvin L, Green J, Layard R, Pilling S, Janecka M. Transparency about the outcomes of mental health services (IAPT approach): an analysis of public data. *Lancet* 2018; **391:** 679–86.
21. Zipursky J, Juurlink DN. Studying drug safety in the real world research. *JAMA Intern Med* 2018; **178:** 1533–34.
22. Ball R, Robb M, Anderson S, Dal Pan G. The FDA's sentinel initiative—a comprehensive approach to medical product surveillance. *Clin Pharmacol Ther* 2016; **99:** 265–68.
23. Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ* 2015; **350:** h1798.
24. Bean DM, Wu H, Iqbal E, et al. Knowledge graph prediction of unknown adverse drug reactions and validation in electronic health records. *Sci Rep* 2017; **7:** 16416.
25. Malik S, Lally J, Ajnakina O, et al. Sodium valproate and clozapine-induced neutropenia: a case-control study using register data. *J Schizophr Res* 2018; **195:** 267–73.
26. McCoy T. A data-driven approach to identification of deliriogenic medications. Academy of Psychosomatic Medicine Annual Meeting 2016; Austin, Texas; Nov 11, 2016.
27. Law SWY, Wong AYS, Anand S, Wong ICK, Chan EW. Neuropsychiatric events associated with leukotriene-modifying agents: a systematic review. *Drug Saf* 2018; **41:** 253–65.
28. Martin L, Hutchens M, Hawkins C, Radnov A. How much do clinical trials cost? *Nat Rev Drug Discov* 2017; **16:** 381.
29. McGauran N, Wieseler B, Kreis J, Schüler Y-B, Kölsch H, Kaiser T. Reporting bias in medical research—a narrative review. *Trials* 2010; **11:** 37.
30. Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E. Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet* 2004; **363:** 1341–45.
31. Kadra G, Stewart R, Shetty H, et al. Antipsychotic polypharmacy prescribing and risk of hospital readmission. *Psychopharmacology* 2018; **235:** 281–89.
32. Rush AJ, Trivedi MH, Wisniewski SR, et al. acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 2006; **163:** 1905–17.
33. Chekroud AM, Zotti RJ, Shehzad Z, et al. Cross-trial prediction of treatment outcome in depression: a machine learning approach. *Lancet Psychiatry* 2016; **3:** 243–50.
34. Miller M, Swanson SA, Azrael D, Pate V, Stürmer T. Antidepressant dose, age, and the risk of deliberate self-harm. *JAMA Intern Med* 2014; **174:** 899–909.
35. Davis, K. A. S., Farooq, S., Hayes, J. F., John, A., Lee, W., MacCabe, J. H., McIntosh, A., Osborn, D. P. J., Stewart, R. J., & Woelbert, E. (2020). Pharmacoepidemiology research: delivering evidence about drug safety and effectiveness in mental health. *The lancet. Psychiatry*, *7*(4), 363–370. https://doi.org/10.1016/S2215-0366(19)30298-6
36. Rosenheck RA, Krystal JH, Lew R, et al. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. *N Engl J Med* 2011; **364:** 842–51.
37. Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. *J Clin Psychiatry* 2013; **74:** 957–65.
38. Sharma M, Nazareth I, Petersen I. Observational studies of treatment effectiveness: worthwhile or worthless? *Clin Epidemiol* 2018; **11:** 35–42.
39. Uddin MJ, Groenwold RH, Ali MS, et al. Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. *Int J Clin Pharm* 2016; **38:** 714–23.
40. Andrade C. Antidepressants and atrial fibrillation: the importance of resourceful statistical approaches to address confounding by indication. *J Clin Psychiatry* 2019; published online Jan 22. DOI:10.4088/JCP.19f12729.
41. Osborn DPJ, Petersen I, Beckley N, Walters K, Nazareth I, Hayes J. Weight change over two years in people prescribed olanzapine, quetiapine, and risperidone in UK primary care: Cohort study in

*Corresponding Author: **Mohammad Hossein Hooshangi**

THIN, a UK primary care database. *J Psychopharmacol* 2018; **32:** 1098–103.

42. Haukoos JS, Lewis RJ. The propensity score. *JAMA* 2015; **314:** 1637–38.
43. Osborn DPJ, Marston L, Nazareth I, King MB, Petersen I, Walters K. Relative risks of cardiovascular disease in people prescribed olanzapine, risperidone and quetiapine. *Schizophr Res* 2017; **183:** 116–23.
44. Low YS, Gallego B, Shah NH. Comparing high-dimensional confounder control methods for rapid cohort studies from electronic health records. *J Comp Eff Res* 2016; **5:** 179–92.
45. Lipsitch M, Tchetgen ET, Cohen T. Negative controls a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21:** 383.
46. Petersen I, Douglas I, Whitaker H. Self-controlled case series methods: an alternative to standard epidemiological study designs. *BMJ* 2016; **354:** i4515.
47. Hayes JF, Lundin A, Wicks S, et al. Association of hydroxylmethyl glutaryl coenzyme a reductase inhibitors, l-type calcium channel antagonists, and biguanides with rates of psychiatric hospitalization and self-harm in individuals with serious mental illness. *JAMA Psychiatry* 2019; **76:** 382–90.
48. Siskind D, Reddel T, MacCabe J, Kisely S. The impact of clozapine initiation and cessation on psychiatric hospital admissions and bed days: a mirror image cohort study. *Psychopharmacology (Berl)* 2019; **236:** 1931–35.
49. MQ Transforming Mental Health Through Research. How much is spent on mental health research in the UK https://www.mqmentalhealth.org/articles/research-funding-landscape (accessed Oct 12, 2019).

*Corresponding Author: **Mohammad Hossein Hooshangi**