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Lights and shadows of schizophrenia therapy research:

lessons from oral risperidone and olanzapine

Running title: Lights & shadows of schizophrenia therapy research

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Abstract

Background. Recently, patents of several atypical antipsychotics have reached their expiration date.

Aims. The purpose of the study was to highlight whether modifications of economic/scientific factors may be associated with possible changes in the ongoing clinical research on antipsychotic drugs.

Methods. A large systematic analysis was used to depict the time-dependent distribution of published research articles addressing the clinical properties of oral risperidone and olanzapine conventional tablets, two largely prescribed atypical antipsychotics whose patents have already expired in most of the countries.

Results. The systematic analysis indicated that the time-dependent distribution of the selected research articles followed a wave-shape pattern. A dramatic decline of primary and secondary analyses investigating the clinical effects of oral risperidone and olanzapine has occurred in the last decade, complemented by an expected strong reduction in the numbers of industrial-supported clinical studies and a smaller, but significant, decline in the amount of independent research articles.

Conclusions. To date, a greater involvement of independent research seems to be the only realistic chance to properly continue the investigation on the clinical properties of oral risperidone and olanzapine conventional tablets, as well as those of other off-

patent antipsychotic drugs. However, the limits and potentialities of independent research in accomplishing such a demanding and enduring scientific effort should be addressed.

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Antipsychotic, atypical, systematic analysis, patent

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Introduction

Over the past years, patents of several largely prescribed atypical antipsychotics have reached their expiration date and only few active compounds have received the approval for the treatment of schizophrenia symptoms (Albright, 2012; Citrome, 2018; Harrison, 2013). Moreover, the clinical effect of a new generation of antipsychotic drugs devoid of anti-dopaminergic activity still needs further investigation (Girgis et al., 2019; Harrison, 2018; Kinon, 2011; Lin et al., 2018; Siskind et al., 2018; Walling et al., 2016). These circumstances indicate a substantial rearrangement of the relationships between drug development, clinical research and economic factors within the field of schizophrenia therapy, possibly calling for a serious think about the mechanisms which have regulated antipsychotic research over the last decades.

An analysis of the published clinical research on two well-known oral atypical antipsychotics, risperidone and olanzapine, may constitute a useful strategy to collect information on this topic. Oral risperidone (oRISP) and oral olanzapine (oOLA) conventional tablets are among the first atypical antipsychotics which have been introduced into clinical practice. These drugs are still widely prescribed to reduce schizophrenia symptoms and a huge amount of industrial and non-industrial research has investigated and compared their therapeutic properties (Komossa et al., 2010;

Komossa et al., 2011). Patents of conventional oRISP and oOLA tablets have expired, and new formulations, parent compounds and bioequivalent (generic) drugs of these two antipsychotics are already available in the pharmaceutical market of several countries. Using published clinical studies investigating oRISP and oOLA clinical properties, it may then be possible to address some of the most relevant issues which have characterized the evolution of schizophrenia therapy research over the last decades.

The aim of this analysis is to delineate how the scientific/economic effort of clinical research on antipsychotic drugs may change over time. The time-dependent distribution of the published clinical studies investigating the clinical effects of conventional oRISP and oOLA tablets in adult schizophrenic individuals was used to evaluate these modifications.

Methods

Data source and selection criteria

Two extensive systematic PubMed advanced searches were carried out in order to analyze the scientific literature on oRISP and oOLA until 2017. With this purpose in

mind, the antipsychotic names (i.e., “olanzapine” or “risperidone”, respectively) and “Clinical Trial” were used as keywords.

The retrieved articles were further selected by abstract reading, in order to include only English written research articles reporting empirical data or secondary statistical elaborations of the clinical effects induced by conventional oRISP or/and oOLA tablets in schizophrenic individuals. Narrative reviews, comments or other articles with no clinical data elaboration were excluded.

Subsequently, the full content of the collected articles was analyzed, so to ascertain the appropriateness of the previous abstract-based selection procedure and to exclude clinical studies which did not provide/elaborate clinical data on adult schizophrenic individuals (age 18-65 years) treated with oRISP and oOLA tablets.

Data collection

At this point, two datasets were created in order to record data obtained from the research articles investigating the clinical effects of conventional oRISP and oOLA tablets, respectively. In each dataset, the selected articles were identified using Authors’ name, bibliographic references and the year of publication. Moreover, the selected articles were divided in two groups: (i) primary studies (PSs) and (ii) secondary/adjunctive analyses (SAs). PS data were collected so as to monitor the

occurrence of possible modifications in the scientific effort to collect new empirical data on oRISP and oOLA over time. Thus, an article was considered PS only when it provided the first published results of a clinical study, or data coming from an extension of a previously published clinical trial. Research articles reporting sub-, pool-, meta-analyses, database elaborations or adjunctive data of previously published clinical studies were labelled as SAs. Different strategies were applied to reduce the effect of publication redundancy and disaggregation in the identification of PSs (Huston and Moher, 1996). Article text content, study acronyms, trial identifier codes were analyzed in order to verify the originality of the study. Furthermore, each putative PS was compared with other selected research articles included in the dataset, using the first and the last Author name.

To discriminate between industrial supported (IS) and independent research (IndR) studies, the full content of each selected research article was analyzed. A study was labelled as IS when the drug manufacturer/selling company (MC) or any competitor pharmaceutical industry (CC) (including related research foundations) contributed to the study by means of direct funding, sponsored fellowships, employers, structures or any other relevant economic support (drug supplying excluded). A research article was categorized as IndR when only public or no-profit organizations were mentioned and acknowledged for implementing and providing

support to the clinical study. Finally, a research article was labelled as ND (Not Declared) when the source of economic support was not indicated within the article text content.

Data elaboration

A large part of data elaboration referred to the year of publication of the research articles, in order to delineate possible modifications in oRISP and oOLA clinical research over time. The year/s when empirical data were collected (if available) and the number of patients enrolled in each selected PS were also annotated and analyzed so as to better investigate the clinical research pattern of the two antipsychotics (see supplemental data Fig. 1S). An article reporting clinical data on both oRISP and oOLA was counted only once when cumulative analyses of the published clinical research on the two antipsychotics (oRISP+oOLA) were carried out.

Simple linear regression models of the number of published research articles investigating the clinical properties of oRISP+oOLA were applied in the attempt to evaluate possible differences between IS and IndR articles over the last 9 years (2009-2017), when a decline of the number of published research articles on oRISP and oOLA was observed (see supplemental material Fig. 2S).

Dataset recording/extraction and data analyses were performed using OpenOffice (v. 4.1.1.) and R (v. 3.5.2.) software.

Results

The selection procedure identified n=888 and n=840 research articles investigating the clinical effects of oRISP and oOLA, respectively. Overall, n=1304 oRISP+oOLA research articles were selected in this systematic analysis, since n=424 articles had analyzed the clinical properties of both antipsychotics and were present in both datasets.

The time dependent distribution of published articles indicated that the number of oRISP or oOLA studies followed a wave-shape pattern over time (Fig. 1a,b), with the highest number of articles per year being published in 2005-2009. The patterns of the published research on these two antipsychotics were largely superimposable (Fig. 1a,b), as also indicated by the unimodal distribution of oRISP+oOLA research articles (Fig. 1c). A rather stable percentage of research articles showing a direct comparison between oRISP and oOLA clinical properties (mean$\pm$S.E.M.= 29.4$\pm$2.3% vs. oRISP+oOLA articles) was observed starting from 1997.

Two shifted wave-shape curves characterized the distribution of PSs and SAs (Fig. 2). The highest number of PSs was published over 2003-2007, while the maximal production of SAs occurred in 2008-2011 (Fig. 2).

The results of PSs were generally published some years (2.9±0.1 years) after completion of the clinical data acquisition phase.

Wave-shape patterns also characterized the time-dependent distribution of the number of MC- and CC-funded clinical studies investigating the clinical features of oRISP and oOLA, respectively (Fig. 3a,b). The analysis of clinical research on oRISP indicated that the percentage of MC-sponsored studies was globally lower than that of the clinical analyses receiving support from CCs (MC 43.3%; CCs 56.7% vs. all IS oRISP selected articles). The time-dependent distribution of oRISP research showed a progressive inversion of the relative contribution of MC vs. CCs in 2000-2002 (Fig. 3a). On the other side, a large part of the IS studies investigating the clinical effects of oOLA have received support from the MC (MC 67.7%; CCs 32.3% vs. all IS oOLA selected articles), and the numerical superiority of MC- vs. CC-supported articles lasted until 2012 (Fig. 3b). Overall, the research on oRISP+oOLA received maximum cumulative support from the respective MCs in 2003-2007 (Fig. 3c), whereas the contribution of other pharmaceutical companies (OthCs) peaked in 2007-2012 (Fig. 3c).

The distribution of the research on oRISP+oOLA mostly mirrored the pattern of the IS clinical studies (Fig. 4), which constituted 51.5% of the total number of the selected published articles. IndR has also made a remarkable contribution to the characterization of the clinical features of oRISP+oOLA (32.5% of the selected articles). The number of IndR analyses showed a progressive increase until 2008-2009, followed by a moderate decline. The amount of published ND articles (16.0%) peaked in 2001-2004, and their number slowly decreased till 2017 (Fig. 4).

Discussion

A large number of clinical studies have investigated the clinical effects induced by conventional oRISP and oOLA tablets in schizophrenic individuals. Despite the availability of so many studies, the research published so far cannot yet be considered exhaustive in addressing the complex clinical and pharmacological issues related to the use of these two antipsychotic drugs. Recent meta-analyses pointed out that further studies are needed to better characterize the clinical features of oRISP and oOLA, since the influence of genetic, environmental and psychopathological factors on the patient response to these drug therapies is still unclear (Komossa et al., 2010; Komossa et al., 2011; Nasrallah et al., 2015). Moreover, the reasons leading to the occurrence of metabolic side effects and treatment discontinuation during oRISP and oOLA therapy

still need to be further addressed (Soares-Weiser et al., 2013). Keeping these considerations in mind, the observed decline in the numbers of published clinical studies investigating the clinical features of oRISP and oOLA raises obvious concern, since these two drugs are amongst the most largely prescribed antipsychotics for the treatment of schizophrenia symptoms.

The present analysis highlighted that the clinical profiles of oRISP and oOLA have been extensively compared in the recent decades, possibly explaining a substantial convergence between the time-dependent patterns of the clinical research on these two antipsychotics. The percentage of studies investigating the clinical features of both oRISP and oOLA has remained stable over the last years, even in the aftermath of the results of large comparative studies, such as CATIE and CUtLASS (Lieberman et al., 2005; Lewis and Lieberman, 2008; Jones et al., 2006). Thus, a diminished interest in oRISP vs. oOLA head-to-head clinical comparisons can hardly account for the observed decline in the numbers of published clinical studies.

The time-dependent distribution of PS and SA articles may possibly add some insight into the evolution of oRISP and oOLA clinical research. Until 2004-2006, the rapid increase of published PS articles likely reflected the growing scientific and economic interests associated with oRISP and oOLA soon after their introduction into clinical practice. However, it seems that the excitement in investigating the clinical

properties of oRISP and oOLA started to fade after 2006. A clear reduction in the numbers of published PSs can indeed be observed, highlighting a slowdown in the empirical data collection activity. The implementation of the less expensive SAs partially counterbalanced the reduction of published PSs until 2006-2009, but subsequently a general decline of the published investigations on oRISP and oOLA inevitably occurred.

The paucity of new empirical data, thus, seems to primarily account for the decline of the research on oRISP and oOLA. Considering that an average of almost three years elapsed from clinical data collection until the publication of PS results, it appears feasible that the origin of the decline of oRISP and oOLA clinical research may have taken place earlier (2003-2004) than the observed reduction of PSs published studies (2006-2007, Fig. 2), and much earlier than its clear appearance in scientific literature (2009-2010, Fig. 1c).

It cannot be denied that the clinical research on oRISP and oOLA has required substantial human, instrumental and economic resources. To this regard, the contribution of pharmaceutical companies to antipsychotic research has been substantial, albeit not devoid of criticism. Recently, several authors have pointed out that the occurrence of bias may affect the results of industrial-funded clinical trials (Every-Palmer and Howick, 2014; Heres et al., 2006; Montgomery et al., 2004; Perlis et

al., 2005), arguing that an excessive overlap of scientific and economic interests might be counterproductive to schizophrenia therapy research. On the other side, it is undeniable that industrial sponsorship has allowed the implementation of a large number of studies, increasing the availability of clinical data on oRISP and oOLA.

Without passing any judgment on IS research, the present analysis has highlighted that the overlap between scientific and economic interests tends to generate waves of scientific information, in which the research output mostly appears to be rationalized and compressed within the period of intellectual property of the drugs (Albright, 2012; Harrison, 2013). In this framework, it is noteworthy that the time-dependent relative contributes of MC- vs. CC-supported clinical analyses may vary greatly over time (see Fig. 3), questioning the assumption that the competition among pharmaceutical companies may per se ensure the production of promptly counterbalanced clinical results. Most of all, the distribution of oRISP and oOLA research articles indicated that a dramatic decline of published IS studies may occur when patent expiration dates of several antipsychotics converge within a short-time window (2010-2015), even if policy on drug patent expiration may had varied depending on the country (Albright, 2012; Harrison, 2013; Song et al., 2016). Thus, it might be surmised that IS studies do not necessarily guarantee a constant support to clinical research on antipsychotic drugs.

As things stand at the moment, the progress of the research on oRISP and oOLA appears to mostly be dependent on the capability of IndR to implement new clinical studies. In the recent decades, IndR has produced and published many clinical investigations on these two antipsychotics, playing a relevant role in verifying and complementing the results of previous clinical analyses, and providing new and interesting approaches for the characterization of the clinical properties of oRISP and oOLA.

In the last nine years, the IndR scientific production has shown a slower decline than IS research and, if this downward trend still persists, it is expected that IndR will published very few clinical articles on oRISP and oOLA by the end of the next decade (see supplemental material). Conversely, it is highly desirable that the role of IndR in the field of schizophrenia therapy research may become progressively more scientifically relevant in the presence of a disengagement of pharmaceutical companies. Thus, further studies are needed to better evaluate the limits and potential of IndR.

Some limitations should be taken into account when interpreting the results of the present systematic analysis. The large number of research articles selected in the present study cannot be considered exhaustive of all the clinical research addressing the clinical effects of oRISP and oOLA. Particularly, the exclusion of narrative

review/opinion, basic and translational research articles should be taken into consideration.

Information on clinical studies implementation and funding support was only collected from research articles even when available from other sources, since it was considered relevant for coherence of the results to analyze only what has been reported in scientific literature. Furthermore, it was taken into account that time-dependent distribution of ND articles may provide useful data to visualize the effort and awareness of the scientific community and journal editorial policy for transparency issues.

In conclusion, the present analysis for the first time highlighted that wave-shape patterns have characterized the time-dependent distribution of the published research articles investigating the clinical properties of oRISP and oOLA, possibly reflecting modifications in both scientific and economic interests. An alarming reduction of the published research articles addressing the clinical features of the two antipsychotics has occurred in the recent years. This decline was mostly associated with a reduced availability of new empirical data and with a decrement of IS clinical studies. A greater involvement of IndR is certainly desirable so as to properly continue the analysis of the clinical properties of oRISP and oOLA, as well as those of other off-

patent antipsychotic drugs. However, studies are needed to characterize the strengths and weaknesses of IndR in accomplishing such a demanding new role.

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Legends

Fig. 1 - Graphs showing the time-dependent distribution of the published research articles investigating the clinical properties of oRISP (a), oOLA (b), and oRISP+oOLA (c). Articles addressing the clinical features of both oRISP and oOLA were counted only once when the published research on oRISP and oOLA (oRISP+oOLA) was cumulatively analyzed.

Fig. 2 - The graph shows the time-dependent distribution of the published primary studies (PSs) and secondary analyses (SAs) investigating the clinical properties of oRISP+oOLA.

Fig. 3 - Graphs showing the time-dependent distribution of the number of MC- and CC-supported research articles investigating the clinical properties of oRISP (a) and oOLA (b). The number of oRISP+oOLA published articles which were supported by the respective MCs or other pharmaceutical companies (OthCs) is also depicted (c).

Fig. 4 – Graph shows the time-dependent distribution of the number of published IS, IndR and ND research articles investigating the clinical properties of oRISP+oOLA. Furthermore, the curve of the total number of research articles (Total) is depicted.

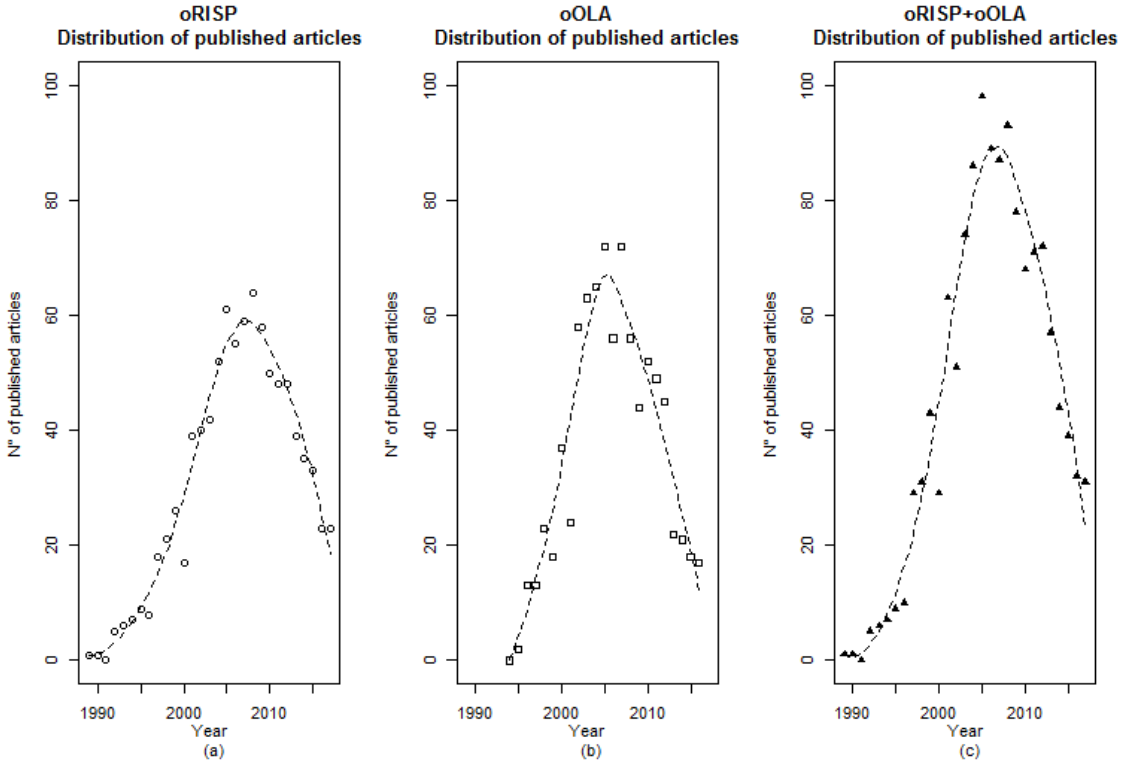
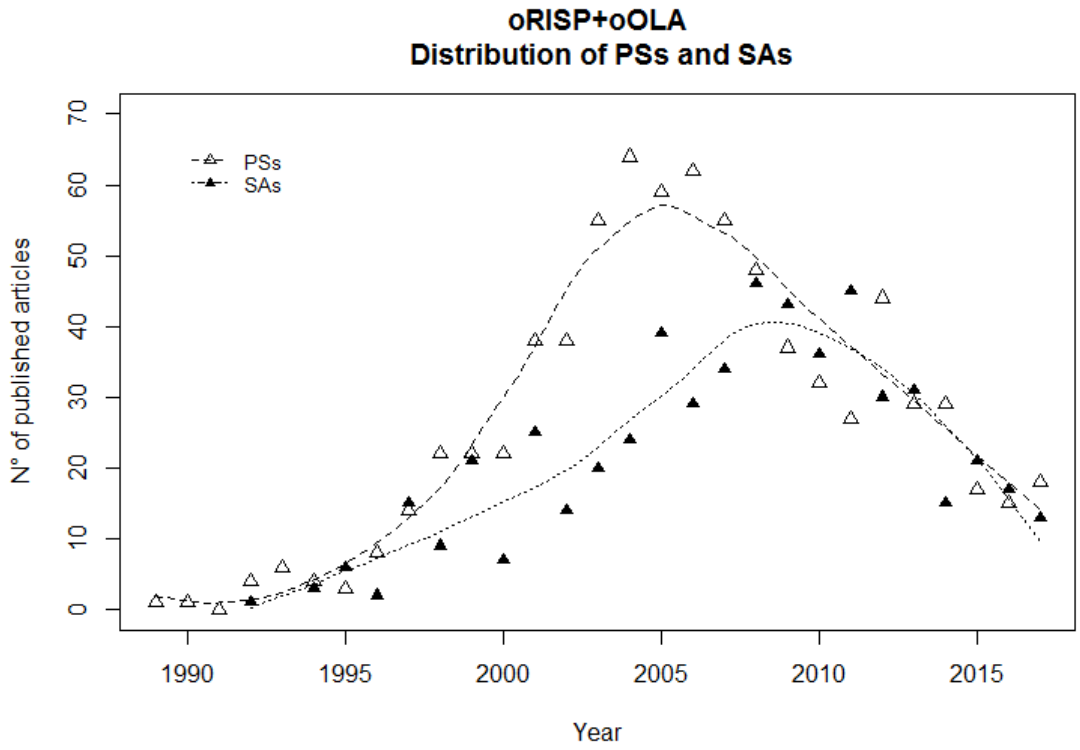

oRISP
Distribution of published articles
oOLA
Distribution of published articles
oRISP+oOLA
Distribution of published articles
N° of published articles
0
20
40
60
80
100
1990
2000
2010
Year
(a)
(b)
(c)

Fig. 1


oRISP+oOLA
Distribution of PSs and SAs
PSs
SAs
N° of published articles
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10
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30
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50
60
70
1990
1995
2000
2005
2010
2015
Year

Fig. 2

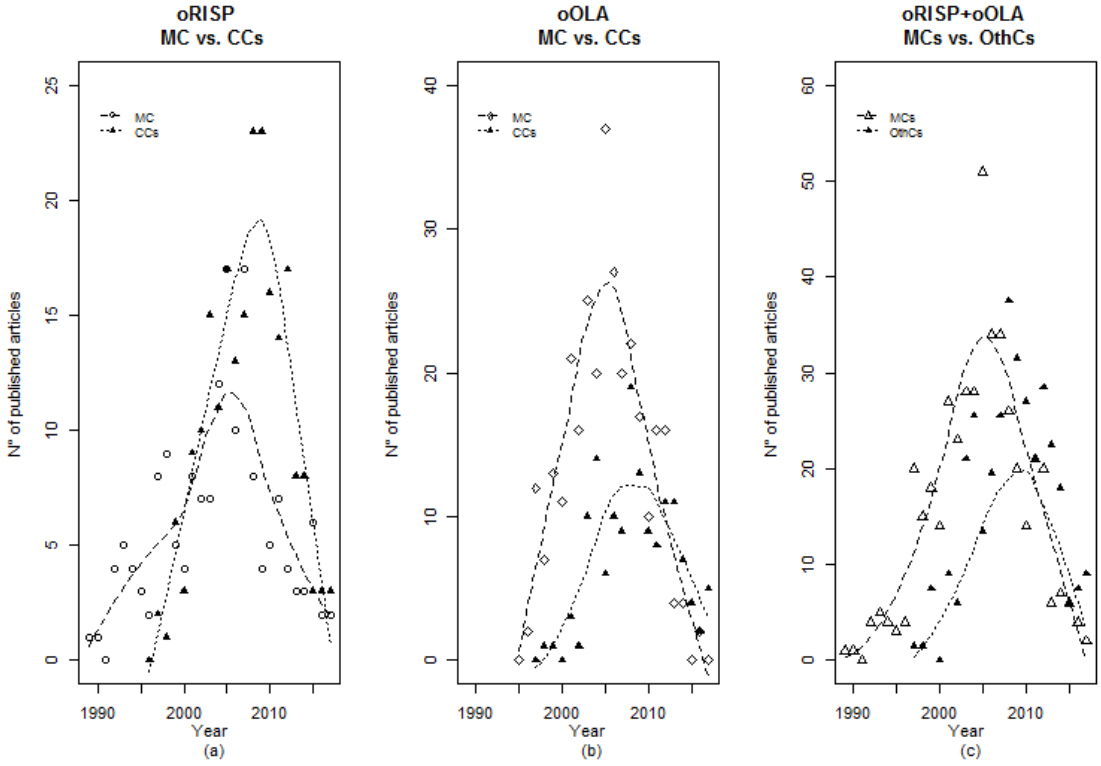
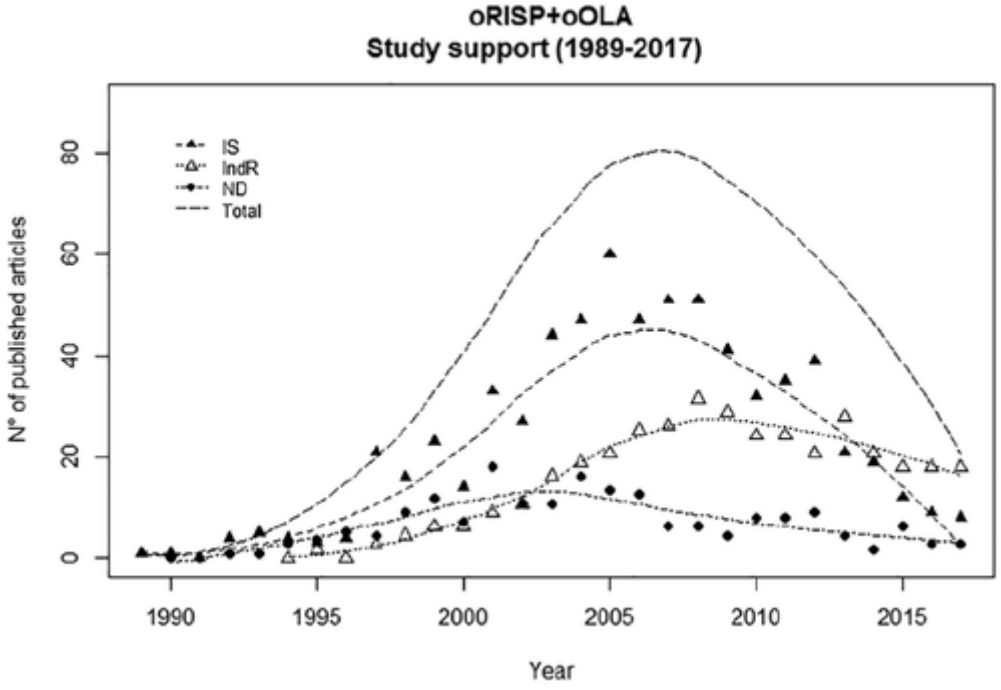

oRISP
MC vs. CCs
MC
CCs
N° of published articles
Year
(a)
oOLA
MC vs. CCs
MC
CCs
N° of published articles
Year
(b)
oRISP+oOLA
MCs vs. OthCs
MCs
OthCs
N° of published articles
Year
(c)

Fig. 3


oRISP+oOLA
Study support (1989-2017)
IS
IndR
ND
Total
N° of published articles
0
20
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60
80
1990
1995
2000
2005
2010
2015
Year

Fig. 4