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Review Article

Clinical Pharmacology in India – A Systematic Review of Research in the Past 5 Years

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The Indian National Science Academy has published two Status Reports on Pharmacological Research (1984 & 2000). The International Council for Science (*ICSU*) National Committee for Pharmacology has commissioned the third status report on Pharmacological Research in India covering the last 5 years. This systematic review covers the status of research in Clinical Pharmacology (excluding pharmacogenomics, pharmacovigilance, pharmaco-economics). We searched PubMed, Scopus and Google Scholar to extract published articles in the various sub-categories like drug discovery and development, clinical trial methodology & biostatistics, medical education, ethics, drug utilization research, therapeutic drug monitoring, pharmacodynamics, therapeutics and systematic reviews. This report presents a summary of the published research in the last 5 years, discusses some of the challenges and how some steps can be taken to raise the standards of clinical pharmacological research in India.

Keywords: Clinical Pharmacology; Status; India; Clinical Research

Introduction

It is hard to imagine that just about 300 years ago, scientists believed that there is a "vital force" without which synthesis of organic compounds was impossible, a theory propounded by Jöns Jacob Berzelius, a Swedish chemist (Melhado, 2016). This belief was challenged by a French chemist, Michel Chevreul in 1816 when he was able to convert an organic compound (soap) to others (glycerol, fatty acids) (Costa 1998). The vital force theory received a major setback in 1828 when Friedrich Wohler, a German chemist, synthesized urea (organic) from ammonium cyanate (inorganic) (Rocke 1999). Although the concept of experimentation (testing of plant extracts on animals and humans) had existed through the works of ancient Egyptians (1600-3000 BC), Sushruta and Charaka (~600 BC), Hippocrates (~400 BC), Aristotle (~350 BC), Galen (130-210 AD), and Ibn Sînâ (980 AD-1037), it is the synthesis of urea, followed by synthesis of acetic acid and other organic compounds from inorganic compounds in the mid-19th century, that we consider to be the starting point of modern pharmacology.

Around this time, in 1847, a professor of pharmacology (Rudolf Buchheim) was appointed at the University of Dorpat (then in Russia) (Scheindlin 2001). He, and his more famous student from Latvia, Oswald Schmiedeberg, founded modern pharmacology as we know it today (Scheindlin 2001).

The sub-division of clinical pharmacology was first documented in 1914 by HH Meyer and R Gottlieb in their book in German - 'Pharmacology, Clinical and Experimental' (Orme *et al*., 2010). The credit for being the first clinical pharmacology only work should go to 'Methodology of Therapeutic Investigation', written in 1932 by Paul Martini (University of Bonn), the first clinical pharmacologist, his contributions shown in Table 1 (Shelley and Baur, 1999).

Clinical pharmacology in the english-speaking world lagged behind and it was twenty years later, in an editorial "The Proper Study of Mankind Is Man", Harry Gold wrote, "Conventional pharmacologic investigations deal chiefly with experiments on

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Table 1: Some important contributions of Paul Martini, arguably the first clinical pharmacologist

Contributions of Paul Martini (1889-1964)
· Coining of the term "clinical pharmacology"
· "N of 1" trial
· Use of matching placebo
· Importance of baseline establishment prior to study initiation
· Importance of controlling extraneous variables to ensure proper new drug versus placebo (or standard) comparisons
· Sample size issues
· Stratification
· Rating scales
· Calculation of probability of efficacy using mathematical models (*Shelley and Baur*, 1999)

laboratory animals..... This contribution is of paramount importance ..... (but) there is a specific aspect of pharmacology which needs more widespread attention, namely, that involving investigations with the participation of the patient, clinical pharmacology" (Gold 1952). Many of us erroneously believe this to be the first use of the phrase 'clinical pharmacology' having been alluded to by Meyer and Gottlieb and used by Martini earlier.

What followed was the golden period of clinical pharmacology - the 1960s. Three landmark books, Goodman and Gilman's 'The Pharmacological Basics of Therapeutics', Laurence's textbook 'Clinical Pharmacology' and Dilling's 'Clinical Pharmacology', the latter being a follow-up of the 1884 'Materia Medica and Therapeutics', along with the journal 'Clinical Pharmacology and Therapeutics', all in 1960 (Orme *et al*, 2010), paved the way for Clinical Pharmacology. With further efforts of Louis Lasagna, Sir Austin Bradford Hill, CT Dollery, and others, including organizations like the WHO and the IUPHAR, departments of clinical pharmacology were established in many countries.

Clinical pharmacology was established in India with the efforts of UK Sheth, Ranjit Roy Chaudhury, PL Sharma, Ashok Vaidya, AS Naniwadekar, and others (Jadhav *et al.*, 2013). The first department of Clinical Pharmacology started in 1960 at Seth GS Medical College & KEM, Bombay (now Mumbai), and the first course in DM – the first of its kind in the world – started at PGIMER, Chandigarh in 1978.

Indian contribution to science in general (Ray *et al.*, 2016; Reddy *et al.*, 1992; Satyanarayana 2000; Talwar and Malhotra, 2016) and clinical pharmacology in particular (Kshirsagar and Kumar, 2011; *Shafiq and Malhotra, 2006*) has been explored earlier along with the two status reports published by Indian National Science Academy in 1984 and 2000. This is the third status report on pharmacological research in the area of "Clinical Pharmacology" during the past 5 years, commissioned by the *ICSU* National Committee for Pharmacology .

Methods

We conducted a systematic review on the status of pharmacological research in the area of "Clinical Pharmacology". Broadly, we categorised Clinical Pharmacology into two areas - Core Clinical Pharmacology and Therapeutics, the scope including research, clinical care, and education and having stakes in academia, governments, regulatory authorities, other agencies like the WHO and pharmaceutical industry (Table 2).

Based on this, we categorised our search into the following areas: drug discovery & development, clinical trial methodology & biostatistics, medical education, ethics, drug utilization research, TDM, pharmacodynamics, therapeutics and systematic reviews.

Selection Criteria

For the purpose of this review we selected research articles based on the following selection criteria (Table 3).

Table 2: Some components of clinical pharmacology

Core Clinical Pharmacology	Therapeutics
· Clinical pharmacokinetics (PK) & Pharmacodynamics (PD)·	· Autonomic nervous system
· Pharmacogenetics	· Central nervous system
· Adverse drug reactions, drug interactions & pharmacovigilance	· Cardiovascular system
· Therapeutic Drug Monitoring (TDM)	· Respiratory system
· New drug development process	· Gastrointestinal system
· Rational use of drugs and drug utilization research	· Nephrology
· Drug prescribing in various populations	· Endocrinology
· Prescription audit	· Reproductive system
· Pharmacoeconomics	· Dermatology
· Clinical trials	· Ophthalmology
· Biostatistics	
· Regulations	
· Bioethics	
· Medical education	
· Systematic review, meta-analysis & Evidence based medicine	

Table 3: Criteria for selection of clinical pharmacological research in the systematic review. *Medical databases that were searched included PubMed, Embase, Scopus, the Cochrane Library and Google Scholar. Biosis Citation Index and Web of Science Core Collection were not searched

Inclusion criteria
- Published research in the field of clinical pharmacology
- The journal publishing research should be indexed in a database*
- Period of publication from January, 2013 to May, 2017, both years inclusive
- Work should have been carried out in India
- At least one author should be pharmacologist

Exclusion criteria
- Research in the areas:
  - Pharmacogenomics
  - Pharmacovigilance
  - Toxicology
  - Pharmacoeconomics
  - Antimicrobial drugs
  - Tropical diseases
  - Cancer chemotherapy
  - Traditional medicine
- Conference abstracts
- Research funded by pharmaceutical industry

Search Strategy

We searched PubMed using keywords pharmacology, India, clinical, humans individually as well as using the Boolean character AND. We also performed a Scopus search for institutions widely considered amongst the top in India. In order not to miss important contributions we also searched PubMed, Scopus and Google Scholar by names of senior pharmacologists/ clinical pharmacologists of the country.

The titles were screened to identify potentially suitable research for inclusion, followed by the author affiliations to find out if at least one of the co-authors is a pharmacologist. Abstracts were reviewed next to select the articles and full texts were retrieved for papers found suitable. Review articles were screened to find any articles that might have been missed. Both the authors independently conducted these searches and the results were collated.

Results

This systematic review involved screening of thousands of articles in the various databases, PubMed search results are shown (Table 4).

Table 4: Results of PubMed search conducted on 11.05.2017

Keywords	No. of articles
Pharmacology AND India	28140
Pharmacology AND India AND humans	14012
Clinical AND Pharmacology AND India	4296
Clinical AND Pharmacology AND India AND humans	2912

AIIMS, New Delhi was the top institution with respect to total number of publications during this period, followed by PGIMER, Chandigarh (Table 5). The other institutions that published >1000 papers during the evaluation period are also shown (Table 5). Searches from other databases are not shown as they do not differ substantially.

Table 5: Yearwise publications identified by Scopus in topmost institutions. Institutions having more than 2000 publications in this period shown. *Shows as Chhatrapati Sahuji Maharaj Medical University in Scopus. #Data till mid-May

Institution	Yearwise publications in Scopus					Total
	2013	2014	2015	2016	2017#	
AIIMS, New Delhi	1492	1749	1685	2145	676	7747
PGIMER, Chandigarh	1252	1341	1237	1382	470	5682
KGMU, Lucknow*	678	484	413	468	129	2172
SGPGI, Lucknow	459	459	427	526	183	2054
CMC, Vellore	487	588	447	373	152	2047
Kasturba Medical College, Manipal	382	416	339	544	150	1831
JIPMER, Puducherry	270	367	357	355	125	1474
Seth GS Medical College and KEM Hospital	307	363	342	346	125	1413
Maulana Azad Medical College, Delhi	324	320	288	278	58	1268
Banaras Hindu University Institute of Medical Sciences	270	288	222	210	34	1024

Central Drug Research Institute, *Lucknow has more than 1100 publications ranging from in-silico exploration through in-vitro to animal to human studies during this period but a detailed evaluation was not done – it being an institute for drug discovery/development – and the readers are referred to* http://www.cdri.res.in/publicationsearch.aspx for further information.

New Drug Discovery and Development

In a collaborative work between CSIR and National Institute of Pharmaceutical Education & Research, Hyderabad, new rhodanine derivatives were synthesized and found to be active against several cancer cell lines (HGC, gastric, breast and prostate cancer) at micromolar concentrations (Ramesh *et al.*, 2014). CSIR-Indian Institute of Chemical Technology, Hyderabad also designed, synthesized and evaluated 4-carboxamide derivatives as CDK1/Cdc2 inhibitors, which were found to have potent growth inhibitory activity against human cancer cell lines like MIAPaCa-2, MCF-7 and HeLa (Reddy *et al.*, 2016). Testing of phenstatin/isocombretastatin-oxindole conjugates for their cytotoxic activity against prostate, lung, colon, breast, and liver human cancer cells was also done (Kumar *et al.*, 2016). Cancer Pharmacology Division, CSIR-Indian Institute of Integrative Medicine, Jammu, in collaboration with the University of Pretoria, South Africa, designed and evaluated santonin analogues on PC-3, MCF-7, A-549 and HCT-116 cell lines and found some of them to be promising (Khazir *et al.*, 2015). In a similar work, a series of chalcone linked-1,2,3-triazoles were synthesized and shown to induce apoptosis, G2/S arrest and mitochondrial potential loss cancer lines including pancreatic cancer (Yadav *et al.*, 2017).

We found that many pharmacy colleges were involved in similar work, but most of it was in dry labs and in very few instances pharmacologists were involved. For example, novel COX-1 selective inhibitors as potential antithrombotic, anticancer and neuroprotective agents were evaluated in mouse macrophages cell lines (Balaji *et al.*, 2014).

We had hoped to find at least some of the leads to have progressed further but we found few examples of phase 1 trials during this period. We are involved in the development of a CDRI antimalarial compound (Shafiq *et al.*, 2014) and further studies are continuing.

We, and others have been involved in research involving repurposing of drugs (Achuthan *et al.*, 2014;

Sircar *et al*., 2015) and some examples can be cited where an older idea of using insulin sensitizers for psoriasis (Shafiq *et al*., 2005; Mittal *et al.*, 2009; Malhotra *et al.*, 2012) has been taken up further by others (Lajevardi *et al.*, 2014; Hafez *et al.*, 2015; Singh *et al.*, 2016). Febuxostat was shown to slow eGFR decline in patients with chronic kidney disease progression (Sircar *et al.*, 2015). We recently showed that probiotic therapy can decrease severity of liver disease and hospitalization in patients with cirrhosis (Dhiman *et al.*, 2014).

Clinical Trial Methodology and Biostatistics

We could retrieve some isolated examples to include in this important category. For example, the critical issue of healthy volunteers taking part in phase I clinical trials of anticancer drugs was discussed (Gupta *et al.*, 2012) particularly with respect to novel, safer options. Phase I trial is a category of research that can typically be planned and conducted by clinical pharmacologists only and all students of clinical pharmacology should gain practical experience of phase 1 trials during their training so that they can actually see what kind of issues are encountered while conducting phase 1 studies. Since few phase I trials are ongoing at a given point of time in India, we had proposed the design of a mock phase I trial as an educational tool for residents (Malhotra *et al.*, 2006), an idea that received little support (Peng *et al*., 2008), much less than we anticipated by 2017.

Another aspect that the clinical pharmacologists should pay attention is that of negative studies. Their publication is useful for many stakeholders as they provide useful information although their reporting is problematic (Malhotra *et al*., 2004). In this regard an interesting analysis showed that negative studies published in prominent Indian medical journals fail to adequately report statistics and methodologies leading to difficulties in appraising them (Charan and Saxena, 2014).

Theoretical work on statistical aspects of clinical trial should be undertaken as it is too important to be ignored. We have proposed that superiority trials should be planned and reported by having a superiority margin similar to non-inferiority margin (Shafiq and Malhotra, 2015) and showed how results of some trials should be interpreted using superiority margin which can change significant results to non-significant (Shafiq and Malhotra, 2016).

Although several groups have in the past worked on designing new tests for clinical pharmacological screening of drugs, there were only a few publications on this topic during the evaluation period. New computerized psychometric test batteries (Pilli *et al.*, 2013) and computerized stroop test (Pilli *et al.*, 2013) have been tested for evaluation of psychotropic drugs**.**

Medical Education

Novel teaching methodologies like case-based learning (Kamat *et al.*, 2012) and module for parenteral drug administration for Pharmacology undergraduates (Devi *et al.*, 2013) have been evaluated. One study evaluated the effectiveness of a mentored student project to assess and promote students' attitudes towards research, which led to inter-departmental and inter-institutional collaborations, 29 publications and conference presentations (Devi *et al*., 2015). Need for modifying the current training for undergraduates and postgraduates has been suggested (Kshirsagar *et al.*, 2013; Ananthakrishnan *et al.*, 2012).

Ethics

Informed consent is a key component of clinical research and several aspects have been evaluated – reasons for refusal (Thaker *et al.*, 2015); factors that motivate participation in research (Doshi *et al.*, 2013; Kamath *et al.*, 2014); consent comprehension (Kamath *et al.*, 2014; Shafiq and Malhotra, 2012). We had earlier designed and evaluated a tool for comprehension of informed consent forms (Bhansali *et al.*, 2009; Arora *et al.*, 2011), which await further testing. Violation of publication ethics in manuscripts was recently analysed (Parasuraman *et al*., 2015). Unethical advertising of medicines also has been a topic of interest (Nath *et al.*, 2014).

Rational use of Drugs, Drug Utilization Studies and Prescription Audit

The maximum number of studies were found in this category, even a systematic review has been done (Bachhav and Kshirsagar, 2015). These studies were hospital-(Mittal *et al.*, 2014) or ward- or unit-oriented, for instance medical emergency (Dhamija *et al*., 2013; Kaur *et al*., 2014), CCU (Kunnoor *et al*., 2014), disease (eclampsia)-oriented (Kumar *et al*., 2014); although we found an interesting study that focused

on one drug, pioglitazone (Pai *et al*., 2016). The late Prof. RR Chaudhary had asked us to conduct a drug utilization study to provide background data so that appropriate amendments regarding drug procurement and dispensing policies can be made (Singh *et al*., 2010) although we did not find recent studies conducted for this purpose.

The issues of drug pricing (Kotwani, 2013; Kshirsagar, 2016; Bhagat *et al*., 2017), and availability and affordability of essential medicines (Kotwani, 2013) have been areas of concern highlighted by several authors. A study in chronic kidney disease showed that medication non-adherence was seen in 34% patients, the commonest cause being high cost (21.3%), followed by complex dosing schedule (20%), and fear of adverse effects (16%), two-thirds were unaware about importance of adherence (Sontakke *et al*., 2015).

An audit of 1170 prescriptions showed that 80% contained 1647 Fixed-Dose Combination formulations with an average of 1.41 per prescription and most of them were irrational or banned (Balat *et al*., 2014). High medication error rates of 42% (in 500 patients) was seen in one study which included prescription errors (55%), transcribing errors (24.5%) and administration errors (21%) (Mathaiyan *et al*., 2016) whereas another study reported error rates of 22.4% and 11.4% for outdoor and indoor patients, respectively (Thakur *et al*., 2013). One interesting study found gross deficiencies in which pharmacogenetic information is provided in Package Inserts (Pai and Kshirsagar, 2016).

Therapeutic Drug Monitoring (TDM)

The maximum number of studies were found in the antiepileptic drugs category. One study showed that although TDM helped in distinguishing nonresponders due to noncompliance, the "reference range" of the drugs did not reliably predict breakthrough seizures or toxicity (Harivenkatesh *et al*., 2015). The latter finding had been seen previously in a study in which among patients clinically suspected of having phenytoin toxicity, only 59% had plasma concentrations above the reference levels (Taur *et al*., 2013). Another study emphasized the need for monitoring the serum levels of even newer antiepileptics like levetiracetam as its levels decreased by about 57% when enzyme inducers were used concomitantly (Gupta *et al*., 2016). Investigations into correlation between serum and saliva levels of carbamazepine, phenytoin, phenobarbital and valproate showed although there is a significant association when monotherapy or bi-therapy is used, it does not exist with poly-therapy (Dwivedi *et al*., 2016; Dwivedi *et al*., 2014).

One study evaluated whether serum creatinine rise after high-dose methotrexate in children with non-Hodgkin lymphoma or acute lymphoblastic leukemia can predict methotrexate clearance (Tiwari *et al*., 2015). Although there was a positive correlation between plasma methotrexate levels with serum creatinine, cut-off values to determine delayed clearance of methotrexate could not be established. Change in creatinine but not delayed methotrexate clearance predicted hematological toxicity. An observational study showed that maintaining the AUC of mycophenolic acid between of 30-60 mg.h/l in Indian renal transplant patients provides adequate clinical benefit and has minimal adverse effects (Sarangi *et al*., 2012).

An interesting study looked at whether splitting of adult tablets for pediatric use provides adequate content uniformity of four antiepileptic drugs (Nidanapu *et al*., 2016). Of the 1098 split tablet parts analyzed, nearly half were above the specified limit, leading the authors to recommend that pediatric dosage formulations and not adult split-tablets should be used in children.

Pharmacodynamics

Non-invasive evaluation of endothelial function in healthy volunteers (Reddy *et al*., 2017), patients with cardiovascular disorders (Gujjarlamudi *et al*., 2013; Pathapati *et al*., 2013) and chronic kidney disease (Annavarajula *er al*., 2012) has been found to be an attractive option it though is still unclear whether it can replace invasive methods.

Studies done to assess cardiovascular risk by evaluating sympathovagal imbalance (low-frequency to high-frequency power of heart rate variability ratio), and other markers like body mass index, blood pressure variability, autonomic function tests, insulin resistance, lipid profile, inflammatory markers and baroreflex sensitivity were significantly altered in young prehypertensives (Pal *et al*., 2013), first-degree relatives of type 2 diabetics (Pal *et al*., 2013),

pregnancy-induced hypertension (Sudha *et al.*, 2016) and in males (Pal *et al.*, 2014).

Therapeutics

Lipid-lowering therapy has been an important field of research worldwide during the past decade. Fixed-dose combination of atorvastatin plus ezetimibe was shown to significantly reduce LDL-cholesterol by an additional 19.9 mg/dL compared to atorvastatin monotherapy in a single-centre trial (Padhy *et al.*, 2013). We were part of a multicentric IMPROVE-IT trial that compared simvastatin (40 mg) and ezetimibe (10 mg) with simvastatin (40 mg) and placebo. It showed an additional 16 mg/dL LDL-C lowering and an absolute risk difference of 2% (HR 0.936; 95% CI 0.89 to 0.99; P=0.016) in favor of the combination for the composite primary endpoint of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalization, and coronary revascularization (Cannon *et al.*, 2015).

Although based on data from several studies and a meta-analysis (Sattar *et al.*, 2010), the USFDA pointed to increased risk of diabetes with statins (USFDA 2012), no effect on pancreatic beta-cell function and insulin resistance in type 2 diabetics was seen one study (Goyal *et al.*, 2014), which could be due to the lower statin dose or small sample size.

An observational study evaluated the association between antihypertensive therapies and glycaemic control and showed that â-blockers and thiazides increase the risk of type 2 diabetes mellitus whereas calcium channel blockers surprisingly lowered the risk, while ACE inhibitors and ARBs were neutral (Ahmad *et al.*, 2014). Whether fixed-dose combination comprising aspirin, statin, and 2 blood pressure-lowering agents versus usual care improve adherence was evaluated in the UMPIRE trial (Thom *et al.*, 2013) of which we were a part. The combination group showed significantly better adherence (86%) vs usual care (65%) and small but statistically significant improvements in SBP and LDL-C without differences in serious adverse events or cardiovascular events (Thom *et al.*, 2013).

Patients with epilepsy on monotherapy had a better quality of life as compared to those on polytherapy was the obvious conclusion of one study (Pimpalkhute *et al.*, 2015). An observational study to evaluate the role of clobazam in epilepsy found that it was used in 132/417 (31.7%) patients, out of whom 3.6% discontinued, common adverse effects being drowsiness, fatigue, headache, memory decline, irritability, abdominal pain and dizziness (Joshi et al., 2014). In a pharmacodynamic study using resected hippocampal tissue from patients with mesial temporal lobe epilepsy, spontaneous excitatory postsynaptic currents were found to be 28% higher as compared to non-epileptic controls, suggesting the role of enhanced endogenous activity of NMDA receptor in causing neuronal excitability (Banerjee *et al.*, 2015).

One study showed that symptoms of depression in patients with subclinical hypothyrodism improved with levothyroxine therapy (Vishnoi *et al.*, 2013). Another study showed that 20% (47/230) medical students were found positive for substance abuse, the most common reasons for taking drugs stress relief (72%) and celebration (72%), with about 60% making effort to quit (Arora *et al.*, 2016). The safety and efficacy of tranexamic acid in controlling haemoptysis was shown in a single-centre, randomized clinical trial, the main effect being on quantity of blood loss (34 mL versus 90 mL with placebo) leading the authors to recommend it as bridging therapy before definitive intervention (Bellam *et al.*, 2016).

Formulation of Guidelines

We are aware of the role of many pharmacologists and clinical pharmacologists as Chairs and Members of the various committees in regulatory affairs, essential medicine list formulation, project review committees and ethics committees. We have in addition been involved in preparation of national guidelines for diagnosis and management of asthma (Agarwal *et al.*, 2015) and chronic obstructive pulmonary disease (Gupta *et al.*, 2014).

Systematic Review and Metaanalysis

A large number of systematic reviews/metaanalyses were published in India during the study period. Although traditionally viewed as a clinical pharmacologist/statistician domain, we found several by clinicians (orthopedics, neurology, pediatrics, pulmonary medicine), pharmacists, and even CROs. There was no pattern in the publication and we found systematic reviews/metaanalyses on various topics, for e.g., angina (Kaur *et al.*, 2014), neuropathic pain

(Rudroju *et al.*, 2013), HDL-rasing drugs (Kaur *et al.*, 2014), preoperative statins (Singh *et al.*, 2013), serratiopeptidase (Bhagat *et al.*, 2013), citicoline (Agarwal *et al.*, 2017), schizophrenia (Andrade *et al.*, 2015), familial hypercholesterolaemia (Malhotra *et al.*, 2014), neonatal sepsis (Jaiswal *et al.*, 2016), psoriasis (Malhotra *et al.*, 2012), and zinc (Das *et al.*, 2012). An interesting review identified 91 resources (databases/registries/electronic medicalrecords/ electronic healthcare records/hospital information systems) described in outcomes research studies conducted in India and showed that Registries (68%) and Databases (25%) were the commonest resources and were mainly established in Maharashtra (21%), Tamil Nadu (12%), and Chandigarh (9%) (Shah *et al.*, 2013).

Discussion

A historical perspective on clinical pharmacology was provided for the younger generation of clinical pharmacologists as well as to emphasize the role of some of the less well-known but relevant scientists and events.

That AIIMS, New Delhi and PGIMER, Chandigarh were the most prolific institutions with respect to number of publications, and by a large margin, comes as no surprise, and is not a new finding. However, we did not adjust the number of publications with number of faculty in these institutions nor did we looked at the impact of those publications, which could be a topic of another review.

We believe that activities associated with new drug development are the most important among the many roles that clinical pharmacologists play – that is why this was the first field we analyzed. A century ago we needed few, if any, clinical pharmacologists since there were few chemicals to be evaluated, as exemplified below (Friedman, 1997):

"Well my old friend,..... how goes it in chemistry?"

"It is asleep. Nothing new ....."

"If one is unable to produce new things ..... it seems you are reduced to inventing new names"

Now there are thousands of molecules being, or waiting to be, screened, tested, and developed as drugs, which requires more and more clinical pharmacologists, as exemplified by the statement of The Wellcome Trust in 2007 - 'There is an urgent need to develop individuals who have the ability to combine a firm grounding in the principles of basic and clinical pharmacology with the most modern research technologies to address complex (patho) physiological questions' (Aronson *et al.*, 2008). Our search showed that some attempts are being made to identify novel targets, screen and develop new molecules in India at many places but they were mostly isolated attempts, and involvement of pharmacologists was minimal. Furthermore, the collaborative, multidisciplinary efforts that are needed to bring a molecule to the market were inadequate. There were hardly any phase 1 or proof-of-concept clinical trials nor too many repurposing trials – domains in which clinical pharmacologists should be leading. We hope that the change in regulation that academic trials for new indications will not need regulatory approval (CDSCO 2015) might improve the repurposing scenario.

The second in order of importance we consider development of clinical trial methodology & biostatistics, and being theoretically solid, our clinical pharmacologists are capable of making important contributions. Unfortunately, we did not find a great deal of work in this area. Equally important is research in medical education and although we did find some publications, they were hardly groundbreaking. Research in ethics is another area where clinical pharmacologists should provide leadership. Since ethical concerns in India are quite different from the developed countries in many aspects, we had hoped to find a great deal of literature. Although there were some publications, they were mostly small, single-centre studies. We osbserved similar situation in other hard core clinical pharmacology fields like TDM and DUS, although it was better for the latter.

One would expect several landmark trials to be published in India keeping in view our so-called traditional strengths – large patient pool, trained physicians, english language and so on, but most of them were single-centre trials with small sample size, and hardly first-of-kind. There was a great dearth of large, multicentric trials that can potentially alter clinical practice. Although greatly needed and recommended (Shafiq *et al.*, 2009), we did not find

good, large, simple, pragmatic trials contributed by pharmacologists. Many metaanalyses and systematic reviews were published although not many received good number of citations. There was hardly any work that could be labeled as having societal impact. Even in an area like prescription audit, there was hardly any research that could have an impact, like The EQUIP Study (Dornan *et al.*, 2009) showing 9% prescribing error rates in newly qualified doctors or the PROTECT Study (Ryan *et al.*, 2014) showing 3364 errors in 1700/4710 (36.1%) patient charts – both were government-funded studies. After a similar project of ours was recently turned down by the ICMR, we tried to do it without funding, but could do only limited work.

At the risk of being labelled defeatist and negative, we cannot claim to have found a rosy picture of research in India after a reasonably thorough search of literature. There were few papers that can be called landmark, little research that had an international impact, and not a single field in which we can claim world leadership.

We are not the first to point to such dismal state. A recent analysis (Ray *et al.*, 2016) showed that more than half of our medical colleges did not publish a single paper between 2001-2010. Even the papers that were published had little impact with more than 90% papers receiving less than 25 citations and just 0.5% got more than 100 citations (Talwar and Malhotra, 2016). The status of clinical pharmacology research was no different from the overall research scenario.

There is no dedicated society for clinical pharmacology in India and a Google search yields one Indian Society of Clinical Pharmacology and Therapeutics program for the year 2002 (ISCPT). We are aware of the clinical pharmacology section of the Indian Pharmacological Society, the Indian Society for Rational Pharmacotherpeutics, and the Indian Chapter of the American College of Clinical Pharmacology. Do the clinical pharmacologists not deserve their own active organization? As an example, a small country like Denmark, with 28000 doctors in a population less than 6 million (one fourth of Delhi), having Danish Society of Clinical Pharmacology, which started in 1976 and has 175 members, boasts of clinical pharmacology being an indispensable part of their healthcare system, multidisciplinary/multi-institutional collaborations, development of sub-specialties, societal impact and contributions to world research (Brøsen *et al.*, 2016).

Several factors are responsible for this state of affairs – most of them relate to overall health research in India rather than specifically to clinical pharmacology. Shortage of funding, health research budget in India being less than one dollar per person (Swaminathan 2016), is probably the most important factor. Lack of collaboration is another – several years ago a hope was expressed that the "ICMR/ Department of Health Research, DST, DBT, CSIR/ Department of Scientific Industrial Research and AYUSH will join hands to formulate the appropriate policy and provide funds for a concerted action" (Kshirsagar and Kumar, 2011). In 2014 we had written a proposal to the ICMR for establishing a Consortium for Clinical Trials in India – a proposal liked by, and agreed upon by the former and the current DG, ICMR. Passed by several committees, it lingers on. On a positive note, a Consortium for tuberculosis has been established and has started working.

One aspect specific to clinical pharmacology is that of training. Clinical pharmacologists are medically qualified practitioners (Aronson, 2010), and when DM (Clinical Pharmacology) was initiated, MBBS with MD (Pharmacology) was considered enough, MD in medicine being unnecessary. May be it was unnecessary then – a time when MBBS passouts knew how to practice medicine - now most medical graduates are incapable of independently handling even simple cases (Malhotra 2015). Since it is unlikely that this situation will change in the near future, we propose that postgraduates should spend some time during their 3-year MD (pharmacology), and susbtantial time during DM, working in internal medicine. Although eligible, few clinicians join DM (Clinical Pharmacology) after their MD – we do not know how clinical pharmacology can be made sufficiently attractive to change this. We feel that revision in the DM curriculum is needed (ideally the job of Society) and it should be uniform across all institutions offerning DM if we expect our students to conduct better research.

*We are not aware whether any progress has been made about an interesting idea t*o start an

Institution of Clinical Pharmacology, Pharmaceutical and Translational Medicine (Kshirsagar and Kumar, 2011), which could have tackled some of the manpower issues, both quantitatively and qualitatively. Most of us have heard of seniors talk about infrastructure issues, absence of a research-enabling environment, and lack of incentives for research – we need to address those if we wish to improve (Malhotra and Talwar, 2016).

Another factor that we long suspected and found was that many of us are doing too many things - conducting research in ten different areas - there are hardly any departments and clinical pharmacologists that can claim to have publications in one or two areas only. This is preventing us from doing pioneering research which could be achieved if as individuals or organizations or even country as a whole, we could focus on limited fields.

Several limitations of this study can be pointed out. It was at best a partial systematic review, as many areas, being covered by others, were left out (antimicrobials, pharmacogenomics, pharmacoeconomics, pharmacovigilance). It will be a huge task to summarize and compile all into one document, a task that must be done. Secondly, some subjective element cannot be ruled out - it is impossible to include all the published papers in clinical pharmacology, their numbers being in thousands, and a decision to exclude an article cannot be fully objectivised. We tried to overcome this by making an attempt to include articles published in high impact journals and by looking at number of citations, the latter itself being problematic as a paper published in 2017 will have less citations than one in 2013. It is also possible that we may have simply missed some important contributions, although both the authors independently searched the literature. We can only apologize to those authors whose work has been inadvertently left out. We did write to some of the national leaders in clinical pharmacology asking them to share their own or others' work they considered worth including, but got only a few responses. In our opinion the readers should be encouraged to communicate to us or the editors regarding work they consider important and, if the publisher permits, a supplement can be printed.

In conclusion, in the areas under review, the contribution of clinical pharmacologists to international research was, to put it bluntly, dismal - the only solace being that it is not drastically different from the overall research scenario in the country. Few collaborations (national, international, interdisciplinary), little innovative research, limited societal impact, negligible global contribution, and lack of its own society – all these factors make the current clinical pharmacology scenario bleak, a state of affairs we find totally unacceptable, begging for an urgent, multi-pronged action plan – a mission possible for our subject experts.

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