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Clinical Drug Development in Parkinson's Disease: descriptive and exploratory analysis of success and failure pathways.

Joana Filipa Simões Martins

Orientador:
Prof. Doutor Joaquim Ferreira

Dissertação especialmente elaborada para obtenção do grau de Mestre em Neurociências

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Abstract

Simões Martins, J. (2022). Clinical Drug Development in Parkinson's Disease: descriptive and exploratory analysis of success and failure pathways.

(Under the direction of Ferreira, J.)

Keywords: Clinical Drug Development, Clinical Trials, Parkinson's disease

INTRODUCTION: The pathological hallmark of Parkinson's Disease (PD) is the loss of dopaminergic neurons, most prominently in certain parts of the basal ganglia, and the aggregation of Lewy bodies proteins in remaining nerve cells. The beginning of clinical drug development in PD started with an orally formulation of levodopa in 1967. Since then, clinical trials were essential to understand how safe the treatments are and to bring new compounds to the market with a proven therapeutic effect. Biopharmaceutical companies around the world attempted to develop innovative therapies to achieve unmet medical necessities. Although the numerous advances on drug development in PD, a significant number of clinical trials still fail to produce new and safe medicines. Indeed, less than 10% of the drugs have been approved by regulatory agencies. It is then important to identify factors that contribute to a successful licensing path in regard to PD. Rigorous efforts have been made in the last decades in various areas such as genetic, biochemistry, epigenetic, omics, clinic and imaging to define reliable markers to improve the quality of clinical trials. Can drug-related markers improve the pharmacologic approaches for restoring striatal dopamine in a targeted and physiological manner or to prevent ongoing neurodegeneration and progression of disease?

OBJECTIVES: The principal aim of this thesis is the description of the landscape of PD therapeutic development programs and critically appraise the causes of compound attrition in the distinct stages of drug development, from phase 1 to phase 4 in Parkinson Disease's studies. Why is it elevated the frequency of drug development failures? Why have it been a decrease in the number of approved compounds in the last two decades? Are failures in drug development observed in all phases of drug development including late stages? Are failures related with non-informative early stage trials? To answer these questions, the outcome of this thesis is centered in identifying the reasons for development drug success.

METHODS: This thesis researched 1304 PD clinical trials. The methodology comprehended a literature research, the design of trial selection parameters, the data extraction, the data analysis, the creation of the PDCard Database and the statistical analysis. For that matter, this study used information from clinical trials relating to Parkinson's disease that were recorded on the 3 platforms: *clinicaltrials.gov*, World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) and Australian New Zealand Clinical Trials Registry (ANZCTR). An embedded type database, named PDCard Database, was finally obtained using *criteria* the data extraction and analysis, totaling a sum of 613 interventional studies of G20 – Parkinson's disease. Then an exploratory analysis of success and failure paths was conducted, and success and failure rates for each trial phase were calculated.

RESULTS: PD drug development registry between 2000 and August 2019 was analyzed, and data published in the PDCard Database. By analyzing the database, it is shown that there is a high frequency of drug development failures and there is a decrease in the number of licensed compounds in the last two decades. For that matter, success and failure paths of the 613 clinical trials and 187 tested compounds, in 77496 total participants, are explored. Fifty variables were (i) categorized (ii) systemized and (iii) organized, based on the SPIRIT guidelines. Each of the variables was added manually and extracted from the original publication of the clinical trial or the clinicaltrials.gov, WHO ICTRP and ANZCTZ. Objectively, the database includes 115 clinical trials in phase 1, 23 clinical trials in phase 1|2, 194 clinical trials in phase 2, 19 clinical trials in phase 2|3, 172 clinical trials in phase 3 and 90 clinical trials in phase 4. 42,90% were multicentered studies, while only 13,38% are monocentered. 74.55% of the studies were randomized and 9,79% are non-randomized studies. 67,86% are completed studies, 11,91% are studies in recruiting phase, 9,62% are studies that are not recruiting, 8,16% are terminated studies and 2,45% are withdrawn studies. It is presented that failures in drug development are observed in all phases of drug development including late stages. Effectively, from all the terminated study causes of all studies, in Phase 1 the most important was first milestone was not met. In Phase 2, lack of efficiency was the primary cause. In Phase 2|3, the main reason was that it was unlikely to provide evidence of significant effect. In Phase 3, lack of efficacy was the main reason for terminating the study. Therefore, failures are mostly related with non-informative early stage trials. The majority of the studies (79,93%) have recruited adult or older adult subjects. Only 10.77% of clinical trials studies included healthy subjects. Most of the diseases studied in clinical trials are diseases of the nervous system (IV), totaling 265 studies. Otherwise, 264 of the clinical trials were studying the efficacy and safety of the drug itself, without specifying PD as a condition to the study. The majority of the trials are designed for treatment purpose. Efficacy is the predominating gold at all phases of development in the study population. As the main outcome of this thesis was identifying the reasons for development drug success or failure, two types of paths were compared: the success rate vs the failure rate. The success rate is higher in PostMarketing Surveillance (PMS), i.e. in phase 4 licensed compounds, and is minimum in the transition of the API from phases 2 and 1|2 to phase 3, i.e. before regulatory proofing. Henceforth, 613 clinical trials in PD conducted from 1998 to 2019, and 187 compounds were vastly studied. From these 187 compounds, only 29 passed confirmatory trials and were finally considered successful paths, that allowed drug licensing. Boehringer Ingelheim, Sandoz and GlaxoSmithKline were the big pharma that conducted more studies completing the full drug development program, including postmarketing surveillance of molecules in phase 4. From all the 29 compounds that were tested, 12 were considered new molecular entities. The new molecular entities that were more studied were rasagiline (30,77%), followed by rotigotine, ropinirole and pramipexole. From all the successful 29 approved compounds, 75,44% were tested in a sample of subjects with all stages of PD. Clinical trials that used quadruple blinding (47,22%) are the ones that produced more licensed compounds that passed confirmatory trials, followed by double blinding (38,89%). The parallel assignment (59,65%) was the type of design that produced more approved compounds, followed by single group assignment (26,32%) and crossover assignment (12,28%). The studies (76,79%) that used oral as a preferred route of administration, and tablets as a preferred drug formulation are the ones that approved more compounds passing confirmatory trials. Dopamine receptor modulators, like pure levodopa and levodopa combinations, represent 52,63% of the success path in the last 20 years. In second, monoamine oxidase

modulators (19,30%), like selegiline and rasagiline, were tested in PD drug development. Thirdly, adrenergic receptor modulators (5,26%), like droxidopa and mirabegron, and catechol o-methyltransferase modulators (5,26%), like entacapone and opicapone, were approved compounds that passed confirmatory trials by the regulatory authorities. From the 29 licensed compounds that passed confirmatory trials, 26,32% of the studies conducted were for non-parkinsonians drugs, while 73,68% of the studies conducted were for antiparkinsonian agents. In the past 20 years, and reviewing the successful path, 15 antiparkinsonian agents primarily passed phase 3 and thus showed regulatory proof. After NDA process and approval, only 14 APIs were registered for PD and, subsequently, completed successfully the postmarketing surveillance studies. The successful antiparkinsonian agents are amantadine, apomorphine, carbidopa/levodopa, levodopa, levodopa/carbidopa/entacapone, entacapone, opicapone, pramipexole, rasagiline, rivastigmine, ropinirole, rotigotine, safinamide and selegiline. Those 14 different antiparkinsonian agents were marketed by 16 different sponsors, in 20 different formulations. Novartis was the big pharma licensing more compounds. Contrasting the success paths, the failure paths that forced the suspension of trial before the final phase of the development program are also described. In the last 20 years, the reasons were mainly due to efficacy, safety and financing. Thirty-five compounds failed to succeed phase 3, and six compounds failed to succeed phase 4. The majority of studies that failed to be approved (34%) do not publish the reasons for terminating or withdrawing the clinical trial.

CONCLUSION: The thesis reviewed the state of the art of clinical drug development in Parkinson's Disease from 1998 to 2019. The problematic of exploring the causes for success/unsuccess is a trending topic in neuroscience. Fundamentally, the work of this dissertation responded to the initially defined objectives. It is then expected that this work will lead to new and interesting questions, which might justify a future multivariate analysis of the 50 obtained variables. The landscape of PD therapeutic development programs was probed and the causes of compound attrition in the distinct stages of drug development, from phase 1 to phase 4 in Parkinson Disease's studies were critically appraised. Indeed, there is a decrease on the success of drug development and in the number of approved compounds that passed confirmatory trials in the last 20 years. Moreover, failures in drug development are observed in all phases of development including late stages, but are mostly related with non-informative early stage trials. Two paths were compared: (i) a successful pathway, passing regulatory proof and confirmatory trials, with a success rate of 16%, that allowed the licensing and adequate postmarketing surveillance of 29 compounds; and (ii) a failure pathway with a failure rate of 84%, that led to the suspension of 158 compounds before the final phases of the development program. Finally, from the 613 clinical trials in PD conducted from 1998 to August 2019 and the 187 compounds, only 14 APIs were finally approved and marketed as antiparkinsonians agents. An antiparkinsonian specific success rate is equal to 7%, and an antiparkinsonian specific failure rate is equal to 93%.

Resumo

Simões Martins, J. (2022). Desenvolvimento Clínico de Fármacos na Doença de Parkinson:
análise descritiva e exploratória das vias de sucesso e insucesso.

(Sob a orientação de Ferreira, J.)

Palavras-Chave: Desenvolvimento de Fármacos, Ensaios Clínicos, Doença de Parkinson

INTRODUÇÃO: A marca patológica da Doença de Parkinson (DP) é a perda de neurónios dopaminérgicos, predominantemente nos gânglios de base, e a agregação de proteínas dos corpos de Lewys (LBs) nas células nervosas restantes. O início do desenvolvimento clínico de fármacos na DP começou com uma formulação oral de levodopa em 1967. Desde então, os ensaios clínicos foram essenciais para entender quão seguros são os tratamentos e para trazer novos compostos ao mercado com efeito terapêutico comprovado. Biofarmacêuticas em todo o mundo desenvolvem tratamentos inovadores para cobrir necessidades médicas ainda não exploradas. Contudo, e embora os numerosos avanços no desenvolvimento de fármacos nos últimos 20 anos, ensaios clínicos ainda não produziram um número significativo de medicamentos novos e seguros na DP. Efetivamente, menos de 10% dos medicamentos testados foram aprovados pelas agências reguladoras. É então importante identificar fatores que contribuam para uma trajetória de licenciamento de sucesso. Nas últimas décadas tem sido feito um esforço rigoroso em várias áreas como a genética, bioquímica, epigenética, ómica, clínica e imagem para definir marcadores fiáveis para melhorar a qualidade dos ensaios clínicos. Será que marcadores farmacológicos podem melhorar as abordagens para restaurar a dopamina no núcleo estriado de forma direcionada ou para prevenir a neurodegeneração e progressão da DP?

OBJETIVOS: O principal objetivo desta tese é a descrição dos programas de desenvolvimento terapêutico na DP e a avaliação crítica das causas de atrito dos compostos nas fases distintas do desenvolvimento do fármaco, i.e., desde a fase 1 até à fase 4 dos estudos da DP. Quais as razões para o insucesso no desenvolvimento de fármacos na DP ser elevado? Quais as razões do decréscimo do número de compostos licenciados nas últimas duas décadas? O insucesso no desenvolvimento de drogas é observado em todas as fases de desenvolvimento, incluindo nas fases tardias? Estará o insucesso relacionado com ensaios iniciais não informativos? Para responder a estas questões, o propósito desta tese centra-se em identificar as razões de sucesso no desenvolvimento de fármacos na DP.

MÉTODOS: Esta tese investigou 1304 ensaios clínicos na DP. A metodologia compreendeu uma revisão de literatura, o desenho de parâmetros de seleção de ensaios, uma extração de dados, uma análise de dados, a criação do PDCard Database e a análise estatística. Para esse efeito, foram utilizadas informações de ensaios clínicos relativos à doença de Parkinson que estavam registadas em 3 plataformas: *clinicaltrials.gov*, World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) e Australian New Zealand Clinical Trials Registry (ANZCTR). Uma base de dados incorporada, chamada PDCard Database, foi obtida usando os critérios de extração e

análise de dados, totalizando uma soma de 613 estudos de intervenção em G20 – Doença de Parkinson. Em seguida, foi realizada uma análise exploratória das vias de sucesso e insucesso, e foram calculadas as respetivas taxas para cada fase experimental.

RESULTADOS: Os programas de desenvolvimento de medicamentos para a DP entre o ano 2000 e agosto de 2019 foram analisados e os dados publicados no banco de dados PDCard. Ao analisar o banco de dados, verifica-se que há uma alta frequência de insucesso no desenvolvimento de fármacos, bem como uma diminuição no número de compostos licenciados para DP nas últimas duas décadas. Para estudar essa tendência, as vias de sucesso e insucesso dos 613 ensaios clínicos e dos 187 compostos testados, totalizando 77496 participantes, são exploradas. As 50 variáveis foram (i) categorizadas, (ii) sistematizadas e (iii) organizadas, com base nas diretrizes do SPIRIT. Cada uma das variáveis foi adicionada manualmente e extraída da publicação original do ensaio clínico ou dos bancos de dados *clinictrials.gov*, WHO ICTRP e ANZCTR. Objetivamente, o banco de dados inclui 115 ensaios clínicos na fase 1, 23 ensaios clínicos na fase 1|2, 194 ensaios clínicos na fase 2, 19 ensaios clínicos na fase 2|3, 172 ensaios clínicos na fase 3 e 90 ensaios clínicos na fase 4. 42,90% eram estudos multicêntricos, enquanto apenas 13,38% são monocentrados. 74,55% dos estudos foram randomizados e 9,79% são estudos não randomizados. 67,86% são estudos concluídos, 11,91% são estudos em fase de recrutamento, 9,62% são estudos que não estão a recrutar, 8,16% são estudos terminados e 2,45% são estudos desqualificados. São apresentadas falhas no desenvolvimento de fármacos em todas as fases do programa de desenvolvimento, incluindo estágios tardios. Efetivamente, de todas as causas para terminar um ensaio clínico, na fase 1, o mais importante foi o primeiro *milestone* não ser atingido. Na fase 2, a falta de eficiência foi a principal causa. Na fase 2|3, o principal motivo foi que era improvável fornecer evidências de efeito significativo. Na Fase 3, a falta de eficácia foi o principal motivo para o término do estudo. Portanto, as falhas estão principalmente relacionadas aos estudos de fases precoces serem pouco informativos. A maioria dos estudos (79,93%) recrutou indivíduos adultos ou idosos. Apenas 10,77% dos estudos incluíram indivíduos saudáveis. A maioria das condições estudadas nos ensaios clínicos são doenças do sistema nervoso (IV), relacionadas com a condição DP, totalizando 265 estudos. Os outros 264 ensaios clínicos estudaram a eficácia e a segurança do próprio medicamento, sem especificar uma condição relacionada com a DP. A maioria dos ensaios é projetado para fins de tratamento. A eficácia é o *primary gold* predominante em todas as fases do desenvolvimento na população estudada. Como o principal objetivo desta tese foi identificar as razões para o sucesso ou insucesso no programa de desenvolvimento do fármaco, dois tipos de caminhos foram comparados: a taxa de sucesso vs. a taxa de insucesso. A taxa de sucesso é mais alta na vigilância e monitorização pós-mercado, i.e. em compostos licenciados em fase 4, e é mínima na transição do *active pharmaceutical ingredient* (API) da fase 2 e 1|2 para a fase 3, i.e. antes das provas regulatórias. Assim sendo, 613 ensaios clínicos em DP realizados de 1998 a 2019 e 187 compostos foram amplamente estudados. Destes 187 compostos, apenas 29 passaram os ensaios de confirmação e foram finalmente considerados caminhos de sucesso, que permitiram o licenciamento do fármaco. Boehringer Ingelheim, Sandoz e GlaxoSmithKline foram as grandes empresas farmacêuticas que conduziram mais estudos completando a totalidade do programa de desenvolvimento do fármaco, incluindo a vigilância e monitorização pós-mercado de moléculas em fase 4. De todos os 29 compostos testados, 12 foram considerados novas entidades moleculares. As novas entidades moleculares mais estudadas foram a rasagilina (30,77%), seguida pela

rotigotina, ropinirol e pramipexol. De todos os 29 compostos aprovados, 75,44% foram testados numa amostra de indivíduos em todas as fases da DP. Os ensaios clínicos de quadrupla ocultação (47,22%) são os que produziram mais compostos licenciados por ensaios confirmatórios, seguidos pelos de ocultação dupla (38,89%). Os estudos paralelos (59,65%) foram o tipo de desenho que produziu mais compostos aprovados, seguidos pelos estudos de grupo único (26,32%) e pelos estudos cruzados (12,28%). Os estudos (76,79%) que utilizaram a via oral como via preferencial de administração e comprimidos como formulação preferida foram os que tiveram mais sucesso nas fases confirmatórias do programa de desenvolvimento do fármaco. Os moduladores dos recetores de dopamina, assim como as formulações puras de levodopa e as combinações de levodopa, representam 52,63% das vias de sucesso nos últimos 20 anos. Seguidamente, os moduladores da monoamina oxidase (19,30%), como a selegilina e a rasagilina, foram os compostos testados com mais sucesso. Em terceiro lugar, os moduladores de recetores adrenérgicos (5,26%), como a droxidopa e o mirabegron, e os moduladores da catecol o-metiltransferase (5,26%), como o entacapone e o opicapone, foram os compostos aprovados pelas autoridades reguladoras com mais sucesso. Dos 29 compostos licenciados e comercializados que passaram nos ensaios confirmatórios, 26,32% dos estudos que foram realizados foram para medicamentos não parkinsonianos, enquanto 73,68% dos estudos que foram realizados foram para agentes antiparkinsonianos. Nos últimos 20 anos, e resumindo as vias de sucesso no programa de desenvolvimento, 15 agentes antiparkinsonianos passaram primariamente na fase 3 e, portanto, completaram as provas regulatórias. Após o processo e aprovação do *New Drug Application*, apenas 14 APIs foram registados para a DP e, subsequentemente, concluíram com êxito os estudos de vigilância e monitorização pós-mercado. Os agentes antiparkinsonianos bem-sucedidos são a amantadina, a apomorfina, a carbidopa/levodopa, a levodopa, a levodopa/carbidopa/entacapona, a entacapona, a opicapona, o pramipexol, a rasagilina, a rivastigmina, o ropinirol, a rotigotina, a safinamida e a selegilina. Esses 14 agentes antiparkinsonianos diferentes foram comercializados por 16 promotores diferentes e em 20 formulações distintas. A Novartis foi a farmacêutica que licenciou mais compostos. Contrastando com os caminhos de sucesso, os caminhos de insucesso que forçaram a suspensão do ensaio antes da fase final do programa de desenvolvimento também são descritos. Nos últimos 20 anos, os motivos foram principalmente devido à falta de eficácia, segurança e financiamento. Trinta e cinco compostos falharam na fase 3 e seis compostos falharam na fase 4. A maioria dos estudos que falharam a completa aprovação após os estudos de vigilância e monitorização pós-mercado (34%), não publicam os motivos da interrupção ou retirada do ensaio clínico.

CONCLUSÃO: A tese revisou o estado de arte do desenvolvimento clínico de fármacos na doença de Parkinson entre 1998 e 2019. A problemática de explorar as causas do sucesso e insucesso é um tópico de tendência na neurociência. Fundamentalmente, o trabalho desta dissertação respondeu aos objetivos inicialmente definidos. Espera-se, então, que este trabalho leve a novas e interessantes questões, que possam justificar uma análise multivariada das 50 variáveis obtidas. O panorama dos programas de desenvolvimento terapêutico da DP foi investigado e as causas de atrito dos compostos nos distintos estágios do desenvolvimento farmacológico, da fase 1 à fase 4 nos estudos da doença de Parkinson, foram avaliadas criticamente. Com efeito, há uma diminuição do sucesso no desenvolvimento de fármacos e do número de compostos licenciados nos últimos 20 anos. Além disso, falhas no desenvolvimento de medicamentos são observadas em todas as fases do desenvolvimento, incluindo em fases mais tardias, que

estão maioritariamente relacionadas a ensaios clínicos não informativos principalmente em estágios iniciais. Duas vias foram comparadas: (i) uma via de sucesso, completando as provas regulatórias e ensaios confirmatórios, com uma taxa de sucesso de 16%, que permitiu o licenciamento e a vigilância e monitorização pós-mercado de 29 medicamentos; e (ii) uma via de insucesso com uma taxa de insucesso de 84%, que levou à suspensão de 158 compostos antes da fase final do programa de desenvolvimento. Finalmente, dos 613 ensaios clínicos em DP realizados entre 1998 e agosto de 2019 e dos 187 compostos, apenas 14 APIs foram finalmente aprovados e comercializados como agentes antiparkinsonianos. A taxa de sucesso específica para agentes antiparkinsonianos é igual a 7% e a taxa de insucesso específica de agentes antiparkinsonianos é igual a 93%.

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Introduction

1. Parkinson's Disease Definition And Disease Progression

Parkinson's disease (PD) was medically defined by James Parkinson in 1817 under the term "shaking palsy" (Jankovic, 2008). This progressive neurodegenerative disorder is predominantly recognized by motor symptoms manifestations as bradykinesia, tremor, rigidity, and postural impairment (Sauerbier et al., 2016).

The degeneration of the dopaminergic neurons in the brain is thought to play a key role in the development of Parkinson's disease. The dopaminergic neurons are susceptible to degeneration because of their extensive branching and the large amounts of energy required to send nerve signals along this extensive network (Mamelak, 2018).

The pathological hallmark of PD is not only the loss of dopaminergic neurons, most prominently in certain parts of the basal ganglia, specifically in substantia nigra, putamen, but also the aggregation of Lewy bodies (LBs) proteins in remaining nerve cells (Alexander, 2004).

Concomitantly to the serious motor signs, numerous non-motor manifestations are also present, such as cognitive impairment, hyposmia, fatigue and psychiatric disturbances such as depression and sleep disturbances. Likewise, sensory symptoms are common, such as pain and tingling, impaired olfactory ability or autonomic dysfunction. This non-motors manifestations and sensory symptoms also have a significant impact on the patient's quality of life (DeMaagd and Philip, 2015).

Thus, and although PD remains clinically defined by midbrain dopaminergic cell loss associated with LBs, it is now recognized that PD has a more widespread impact throughout multiple regions of the nervous system, causing complex non-motor symptoms and associated pathology (Michel, Hirsch, and Hunot, 2016).

PD patients manifest a heterogeneous clinical syndrome and this variability in the clinical phenotype seem to suggest the existence of several subtypes of the disease. Hence, the course of the disease and prognosis differs (Marras and Lang, 2013), and it has been postulated that the various subtypes also have distinct pathogenesis and etiologies (Jankovic et al., 1990; Kouli, Torsney and Kuan, 2018).

Though a consensus has yet to be met, one subclassification primarily based on clinical characteristics suggests two subtypes: a tremor dominant PD and a non-tremor dominant PD (Luo et al., 2017). The patients with tremor dominant PD show mostly motor symptoms and generally respond well to dopamine replacement therapy. However, the patients with a non-tremor dominant PD mainly present a postural instability disorder, i.e. an akinetic-rigid syndrome and an increase of the incidence of the non-motor features (Luo et al., 2017).

Commonly, the motors and non-motor symptoms aggravate over time with the disease progression and this aggravation also exists because of complications associated with long-term levodopa therapy (Noyce et al., 2012). This debility is characterized by the increase of non-motor fluctuations, dyskinesias, but also psychosis, symptomatology that is rather difficult to manage. Non-motor symptoms as sleep disturbances and cognitive impairment are common in early PD stage. However, when these symptoms progress, patients are challenged to a new set of complications. Moreover, in an advanced disease stage, both motor and non-motor symptoms may become resistant to current medications. Postural instability and freezing of gait may lead to falls and fractures, while dementia and hallucinations sometimes warrant care home placement (Kouli, Torsney and Kuan, 2018). These non-motor complications are present in a high percentage of patients with PD after 20 years of diagnosis (Martinez-Martin et al., 2011; Iranzo et al., 2013).

The progression stage and the severity of PD are important factors to consider when taking effective therapeutic decisions. On the one hand, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) provides a comprehensive assessment of disability and disease impairment by evaluating the most pertinent clinical features of PD. On the other hand, the Hoehn and Yahr (HY) scale provide an assessment of disease progression through a staging which ranges from 0 (no sign of disease) to 5 (severe signs of disease) (Hoehn and Yahr, 1998; Goetz et al., 2008).

The Unified Parkinson's Disease Rating Scale (UPDRS) has four parts (Ramaker et al., 2002). Each part has multiple points that are individually scored, using zero for normal or no problems, 1 for minimal problems, 2 for mild problems, 3 for moderate problems, and 4 for severe problems. These scores are tallied to indicate the severity of the disease, with 199 points being the worst and total disability and 0 meaning no disability (Perlmutter, 2009). In 2001, the Movement Disorder Society (MDS) updated the rating scale with involvement from patients and caregivers. The updated scale is referred to as the UPDRS-MDS, and it was published in 2008 (Goetz et al., 2008).

The Hoehn and Yahr scale, named for its authors, was published in 1967 and was the first rating scale to describe the progression of PD (Hoehn and Yahr, 1998). The Hoehn and Yahr scale describes five stages to PD progression. The Hoehn and Yahr scale have since been modified with the addition of stages 1.5 and 2.5 to account for the intermediate course of Parkinson disease. It was designed to be a descriptive staging scale to evaluate both disability and impairment related to clinical disease progression (Goetz et al., 2004).

2. From Levodopa To Opicapone: State Of Art Of The Pharmacological Treatment

The beginning of the levodopa era started when Cotzias and colleagues (1967) discovered an efficient and prolonged effect on the parkinsonian symptomatology in PD patients using an orally formulation of levodopa.

Moreover, in the beginning of 1970, it was discovered that apomorphine, a dopamine agonist, could provide a great improvement on levodopa side effects and loss of treatment efficacy. The dopamine agonists then began to find a place in routine treatment of PD since 1974 (Tolosa et al., 1998). Moreover, at that time, it was discovered that the dopa decarboxylase inhibitor, added to levodopa medication, was capable to reduce the side effects of levodopa treatment and provide a better control of the symptomatology. The first levodopa combination, carbidopa/levodopa, became commercially available in 1975 (Cotzias, Van Woert and Schiffer,1967).

The current commonly treatment given to the PD patients is predominantly based in dopaminergic drugs (Zahoor, Shafi and Haq, 2018). The main current PD treatment is based on levodopa-based preparations created to substitute the dopamine molecule in the depleted striatum. The precursor of dopamine is administered in combination with a dopa-decarboxylase inhibitor which acts to limit some of the side effects, such as nausea (Antonini, et al., 2010; Dixon et al., 2017). These medications are commercially available under the names Duopa®, Rytary® and Sinemet®.

In order to provide a more predictable release of dopamine, not yet possible by oral preparations, one approach is developed to guarantee the dopamine deliver process

in a more physiological manner, that is by using a levodopa-intestinal gel (Abbruzzese et al., 2012). On the one hand, this approach shows benefits in reducing the motor adverse effects of dopaminergic treatment, on the other hand, this approach is a more expensive method and could bring some complications related to the surgery, which is necessary for its placement (Olanow et al., 2014; Zahoor, Shafi and Haq, 2018).

Therefore, the prolonged use of levodopa as main therapy results in significant adverse effects, which form a significant part of the clinical picture in advanced stages of PD. These medications result in problematic dyskinesias (Jenner, 2003; Huot et al., 2013), and significant fluctuations in motor functions, giving the so called on-off phenomenon (Nutt et al., 1984). These medications also result in off-target effects, resulting from their delivery to other areas in the brain than the striatum, which is thought to be the basis for the neuropsychiatric adverse effects that can occur, including hallucinations and impulse control disorders (Ernst, 1969 ; Voon, et al., 2009).

Other great development that came into the market for the treatment of PD in 1978 is called dopamine receptor agonists (Zahoor, Shafi and Haq, 2018). They act stimulating the activity of the dopamine system by binding with the dopaminergic receptors. The major difference between the dopamine receptor agonists and levodopa is that they don't need to be converted into dopamine to produce an effect (Deleu, Northway and Hanssens, 2002). Dopamine agonists such as pramipexole (Mirapex®), rotigotine (Neupro®), and ropinirole (Requip®) are often prescribed as an initial therapy for PD, particularly in younger patients (Contin et al., 2019). In comparison to levodopa, the treatment with dopamine agonists have had a better effect in reducing the incidence and severity of dystonia, dyskinesia and motor fluctuations (Goldenberg, 2008; Ceravolo et al., 2016). However, this type of treatment has side effects that can include nausea and vomiting, peripheral edema, insomnia and hallucinations (National Collaborating Centre for Chronic Conditions, 2006; Goldenberg, 2008).

One of the other options for the treatment of PD patients is the Monoamine oxidase B inhibitor (MAO-B). MAO-B is an isoform of monoamine oxidase that is involved in dopamine metabolism. MAO-B acts by breaking down the dopamine molecule, reducing their activity and promoting an increase of the dopaminergic activity within the striatum, mediated by the endogenous dopamine (Cai, 2014). MAO-B's such as selegiline and rasagiline, commercially available by the names Eldepryl®, Zelapar®, Deprenyl® and Azilect®, are used to relieve motor symptoms in PD patients. Both selegiline and rasagiline are mainly effective in the early stages of PD and they have shown a decrease about 2–3 UPDRS motor score units. They can be used as an initial treatment option, to delay the need for levodopa therapy and to reduce the risk of levodopa-induced motor complications (Zahoor, Shafi and Haq, 2018). Parallelly, they can safely be combined with dopamine agonists, memantine or anti-muscarinic drugs, increasing the anti-parkinsonian effect. They can also be used as adjunctive therapy to allow a reduction in the levodopa dose used and prolonging the duration of levodopa action (Goldenberg, 2008).

In general, monotherapy with MAO-B inhibitors has a lower beneficial effect on PD symptoms than dopamine agonists, but the adverse effects of MAO-B inhibitors are less troublesome than those of dopamine agonists (Giladi et al., 2016). However, they do not treat many of the non-motor features, which are particularly disabling for many patients. MAO-B inhibitors are generally well tolerated, with gastrointestinal side effects being the most common problem (Zahoor, Shafi and Haq, 2018). Other adverse effects include insomnia, dizziness, confusion and hallucinations (Young, Camicioli and Ganzini, 1997; Kujawa et al., 2000; National Collaborating Centre for Chronic Conditions, 2006; Goldenberg, 2008).

More recently, the drug safinamide (commercially named Xadago®) was approved for use in PD patients. Safinamide is a novel medication with both dopaminergic and non-dopaminergic effects, approved first by the European Commission and more recently by the US Food and Drug Administration (FDA) as an adjunctive treatment to carbidopa/levodopa in patients with mid-to late-stage PD and motor fluctuations (Bette et al., 2018). This drug seems to have numerous modes of action, one of which is assumed to act by the inhibition of MAO-B (Stoker, Torsney and Barker, 2018). Safinamide is an add-on medicine usually prescribed when levodopa and carbidopa have a breakthrough of PD's symptoms that were previously under control. Some studies show that adding this drug may help individuals experiencing longer times with reduced or no symptoms (Bianchi et al., 2019). The most common side effects are trouble falling or staying asleep, nausea, falls, and uncontrolled or involuntary movements (Cruz, 2017).

Other types of drug class are the anticholinergic drugs. These drugs reduce the activity of the neurotransmitter acetylcholine, the neurotransmitter that regulates movement, by acting as antagonists at cholinergic receptors (Zahoor, Shafi and Haq, 2018). Drugs as benztropine (Cogentin®) and trihexyphenidyl (Artane®), can be helpful for tremor and dystonia associated with wearing-off effect (Cloud and Jinnah, 2010). Anticholinergic drugs play more of a role in tremor-predominant PD, where they may be used as monotherapy in the early stages. The main role of these drugs is promoting relief of mild movement symptoms, particularly tremors and muscle rigidity (Zahoor, Shafi and Haq, 2018). However, when anticholinergics are used, they are usually in combination with levodopa (Katzenschlager et al., 2002). Potential adverse effects include confusion, cognitive impairment, hallucinations, dyskinetic movements, and memory problems (Katzenschlager et al., 2002).

Another type of medication is amantadine. Amantadine has subsequently been used for the treatment of PD (Tanner et al., 2020), but in recent years it has been found suitable in reducing dyskinesias that occur with dopamine medication. In 2017, an extended-release form of amantadine (Gocovri®) was the first drug approved by the FDA specifically to treat dyskinesia in PD. This new formulation allows a more gradual time to peak plasma amantadine concentration and higher drug concentrations in the morning and throughout the day, the period when levodopa-induced dyskinesia is the most problematic (Paik and Keam, 2018). Amantadine may help mild-stage PD patients in rigidity, rest tremor, and sometimes fatigue, and may offer a short-lived improvement in symptoms (Tanner et al., 2020; Sawada et al., 2010). Although generally well tolerated, the possible side effects associated with the use of amantadine include hallucinations, confusion and impaired concentration (Zahoor, Shafi and Haq, 2018).

Other similar approach called Catechol-O-methyltransferase (COMT) inhibitors can be used to reduce the metabolism of endogenous dopamine (Dezsi and Vecsei, 2017). Catechol-O-methyltransferase (COMT) inhibitors such as entacapone (Comtan®), opicapone (Ongentys®), and tolcapone (Tasmar®) can be used to decrease peripheral levodopa metabolism (Rodrigues and Ferreira, 2017). Inhibitors of COMT preserve the endogenous dopamine levels by reducing its breakdown (National Collaborating Centre for Chronic Conditions, 2006). These types of drugs are predominantly used as adjunctive therapy to levodopa, prolonging their action duration by increasing its half-life and its delivery to the brain. In some patients, this allows managing motor symptoms and reducing the "off time" in comparison to standard levodopa and dopa-decarboxylase inhibitor combinations (Ahlskog, 2003). Entacapone, opicapone and tolcapone are frequently prescribed to the patients that suffer the "end-of-dose wearing off" with levodopa therapy (Nyholm, 2006).

3. Drug Development Process

Preclinical research aimed to answer basic questions about the drug's safety. However, they do not provide enough information for understanding how the drug will interact with the human body.

Clinical trials are thus essential to understand how effective or safe are the treatments, interventions or diagnostic tests in humans. Clinical trials are the source that can provide new information about the diseases, how it manifests and the clinical course that it takes, promoting an increase on drug development knowledge (Akhondzadeh, 2016).

The transition from preclinical research to clinical stages marks a critical turning point in drug development. The scientific goal of drug development is then to bring a new compound to the market with a proven therapeutic effect (David and Kim, 2019). Drug development starts with the identification of a "druggable" target. Lead compounds are identified and are evaluated by testing their potential to interact with the targets, but also their effect on the biological system. When a potentially compound is identified, this investigational new drug becomes a candidate for clinical trials involving human subjects (Honek, 2017).

Clinical trials are conducted throughout different phases, from phase 1 to phase 4, starting from a small number of subjects and extending to large cohorts (Ng, 2015). About 70% of drug candidates move from Phase 1 to Phase 2, in which therapeutic efficacy of the investigational new drug in patients is assessed (Food, U. S., 2017).

Phase 2 studies usually involve numerous patients. The study population is well defined by inclusion and exclusion criteria and established on the dose range determined in Phase 1 (Francillon, Pickering and Belorgey, 2009). During Phase 2, subjects are monitored for detected adverse effects in order to assess the safety profile of the drug. Moreover, these trials frequently determine the optimum dose range to be used in Phase 3 (Friedman et al., 2015; Food, U. S., 2017).

About one third of tested investigational new drugs pass to the phase 3. The phase 3 studies usually have between 100 and 500 patients and they have a longer duration than Phase 1 and 2 studies. This range of time is essential to access the rare and long-term side effects that can occur. The primary aim of this study phase is the confirmation of the therapeutic benefit of the investigational new drug, as well as the safety and efficacy in the proposed indication (Francillon, Pickering and Belorgey, 2009).

Based on the outcome, 25% to 30% of the investigational new drugs progress to the phase 4 (Food, U. S., 2017; Waller and Sampson, 2017). The Phase 4 studies are long-term and usually conducted after regulatory agency approval (post-marketing studies). Phase 4 studies are also known as post-authorization safety studies (PASS) and may be voluntary or imposed by the regulatory authorities. They commonly involve more than 10.000 subjects and aim collecting additional information on safety, efficacy, and new indications.

Consequently, Phase 4 trials assess the drug's real-life effectiveness in a large cohort and provide the opportunity of detecting adverse effects not yet documented. On the other hand, Phase 4 studies may also open up new markets by demonstrating effectiveness for innovative drug indications (Food, U. S., 2017; Waller and Sampson, 2017; Honek, 2017).

4. Successful And Unsuccessful Clinical Trials Exploration

Biopharmaceutical companies around the world attempt to develop innovative therapies to achieve unmet medical necessities. Although numerous advances on technological, scientific and R&D areas were achieved, that would be expected an increase of the efficacy and success of drug development. Contrariwise, a significant number of clinical trials still fail to produce new and safe medicines (Pretorius, 2016).

As an example, data collected between 1990 and 2004 shows that the number of unsuccessful clinical trials has been progressively increasing over the time: from 30% to 50% at Phase 1, from 40% to 70% at Phase 2 and from 20% to nearly 50% at Phase 3. Nevertheless, less than 10% of the drugs have been approved by regulatory agencies (Akhondzadeh, 2016). Although this percentage might seem high, failure of early-phase trails is expected to some extent due to the "exploratory", "proof of mechanism" and "proof of concept" trials type. What is unexpected is the percentage of "confirmatory" phase 3 trials that fail about 50%. Supposedly, if the early-phase trials can provide the necessary criteria for moving a drug to Phase 3, reasonably few Phase 3 trials should fail. However, this has not been happening (Pretorius, 2016).

Across the central nervous system-related trials, it seems that there has been a hesitancy to share critical data. This hesitancy may be one root cause to the remarkably high failure rates of drugs in development phases. For example, the clinical trial failure rate for late-stage Alzheimer Disease therapies from 2002 to 2012 was 99.6%, with 72% of agents failing in Phase 1, 92% failing in Phase 2, and 98% failing in Phase 3 in the period observed (Cummings, Morstorf and Zhong, 2014).

A study from Thomas and colleagues (2016), aimed to assess the trials success rates by measuring the "probability of FDA approval" over ten years (2006-2016). The conclusion shows a very low probability (9.6%) for the progression of a compound from phase 2 until to "the market". Consistently, the lowest transition success rate was in Phase 2 (30.7%), with the second-lowest phase transition success found in Phase 3 (58.1%). Moreover, the time for regulatory review and drug approval for neurology compounds is the longest across all disease areas. Furthermore, the approval drugs in neurological areas are mainly for seizure treatment (39%), Parkinson disease (23%) and neuromuscular disorders (20%) (Kinch, 2015). Collectively, these facts pose considerate pharmacoeconomic challenges for pharmaceutical companies to continue to invest, given the current limited return on investment (Taylor, 2015).

The three most common reasons that drugs or trials fails are efficacy, commercial/financial and safety reasons, as explored above.

A study related by Hwang and colleagues (2016) allowed the access of 640 clinical trials in phase 3 of development with new therapeutic compounds. This study showed that 57% of the failing is due to inadequate efficacy. It seems that the primary cause of trial failure remains the incapability to demonstrate efficacy (Cohen, 2010). The reasons presented are based on inconsistent studies designs, inappropriate statistical endpoints and underpowered clinical trial with a small sample size due to insufficient enrollment (Hwang, et al., 2016).

Hwang and colleagues (2017) also related that 22% of the withdrawn phase 3 studies failed due to lack of funding. The costs required to complete the entire development process from discovery to bringing a drug to market are high. Otherwise, some trials can be underfunded, making them too small and short-lived to provide high-quality evidence and reliable estimates of the long-term balance of risks and benefits, giving them a low opportunity to generate a positive outcome. Underfunded trials are

also more probable to miss the enrollment needed to demonstrate statistical significance at a predefined level of efficacy (Williams, et al., 2015). Patients generally have an expectation that their participation in a trial will lead to an advancement of knowledge based on the trial's successful completion (Lièvre et al., 2001; Crowther, 2013).

On the other hand, the cost of uncovering a safety issue increases at each stage, including post-approval (Tong, Tong and Tong, 2009). Sometimes, due to the sponsor desire to move a drug forward in the clinical trial process, the drug moves quickly from a successful phase 2 trial into phase 3 trial, without the necessary time to pass all the safety details in a phase 3 trials (Shanley, 2016). Eligibility criteria is an important topic to determine the success or unsuccess in a trial. Inclusion and exclusion criteria are often tailored to permit assessments of the efficiency of a treatment in a distinct population. Inclusion criteria identify the characteristics needed for study entry, such as stage of disease or specific pathophysiological features. The eligibility criteria characteristically identify a population in which it is predictable that the effect of the drug can be revealed. Inclusion and exclusion criteria should result in a population that matches statistically the intended general patient population (Heneghan, Goldacre and Mahtani, 2017; Verster et al., 2017).

When designing clinical trials, there is a difficulty in taking a decision between the reduction of heterogeneity, which can cover a finding of the effect, and the production of data that can be generalized to a larger population that needs to be treated. However, study designers must account for additional concerns, including whether or not particular segments of a target population may have numerous comorbidities, leading to a supplementary higher risk of withdrawal and adverse events (Fogel, 2018).

Moreover, study centers have been reporting fewer eligible patients than previously estimated (Bennette et al., 2016; Dickson et al., 2013). A study realized by Bower and colleagues (2009) showed that in 114 trials in the UK, only 31% met enrollment goals. There are numerous studies reporting that sites failed to meet enrollment or failed to enroll any subject at all (Schroen et al., 2010; Honek, 2017). Therefore, study sites with a track record of successful enrolling performance, are more expected to achieve enrollment targets (Getz, 2015). In some cases, there are aspects that can discourage the patient's participation as the location of the study sites. When the participants need to relocate during a study, many of them are not disposed to travel to and from the local study site (McNeely and Clements, 1994).

Patient recruitment and retention are affected negatively when patients are concerned about being assigned to a control group rather than receiving active study drug. Part of this effect may be due to patients having poor knowledge about placebos or what specific treatment is given in the control group (Hughes et al., 2017). In addition, scientific literacy in the general population is limited, leading to difficulty understanding information associated with a clinical trial (Bostock and Steptoe, 2012; Krieger et al., 2017).

Otherwise, it is also important to identify other factors that require attention, which arise even in "successful" trials. These successful parameters including the minimization of protocol deviations (Jalgaonkar et al., 2016), the report of adverse events in peer-reviewed publications (Wieseler et al., 2013), the appropriate outcome measure selection, principally if it is a surrogate measure (Twaddell, 2009), the correct interpretation of a clinically meaningful result versus statistically significant result (Molnar, Man-Son-Hing and Fergusson, 2009), the correct ways to handle the missing data (Kang, 2013), the use of subjective measures that are subject to observer bias (Hróbjartsson et al., 2012), and the importance of a long-term follow-up (Linde et al., 2015; Fogel, 2018).

5. Parkinson's Disease Biomarkers

The term "biomarker" is the abbreviated form of "biological marker" and was defined by the National Institutes of Health Biomarkers Definitions Working Group as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention" (Atkinson et al., 2001).

It is very important to find reliable molecular biomarkers that can distinguish PD from other conditions, monitor its progression, or give an indication of a positive response to a therapeutic intervention (Emamzadeh and Surguchov, 2018).

With regard to PD, rigorous effort has been made in the last decades in various areas such as genetic, biochemistry, epigenetic, omics, clinic and imaging to define a reliable biomarker for the prediction, diagnosis and progression of PD. PD biomarkers can be subdivided into four main types: clinical, imaging, biochemical, and genetic (Yilmaz et al., 2019), briefly detailed above.

5.1. Clinical Biomarkers

The most important clinical diagnostic and prognostic markers in PD are the presence of motor symptoms as bradykinesia, resting tremor and muscle rigidity. They are also crucial for monitoring the response to symptomatic therapy and evaluate disease progression in PD (Postuma et al., 2015).

For the detection of prodromal and early PD stages, non-motor features were also considered, including hyposmia, rapid eye movement, sleep behavior disorder, and constipation (He et al., 2018).

5.2. Biochemical Biomarkers

Biomarkers in body fluids and tissues, as blood, saliva, cerebrospinal fluid, can provide a relatively noninvasive examination of proteins levels and other specific molecules related to the PD disease. Sensitive and selective biochemical biomarkers have an essential role in the detection of prodromal PD as well as in the improvement of an early and accurate diagnoses for a successful treatment in PD patients (He et al., 2018).A large number of studies are interested in demonstrating the mechanisms involved in the development of PD as neuroinflammation, oxidative stress, mitochondrial dysfunction and LBs formation (He et al., 2018).

On the protein level, Van Dijk and colleagues (2013) identified that changes in endolysosomal enzyme activities in cerebrospinal fluid may indicate disease status. Later, Mondello and colleagues (2014) identified that cerebrospinal fluid levels of α-synuclein and UCH-L1 show distinct patterns in parkinsonian syndromes. There are indications that levels of α-synuclein oligomers in cerebrospinal fluid as well as their ratio can be convenient for diagnosis and early detection of PD (Tokuda et al., 2010). They are also evidence that metabolites and peptide levels in plasma and cerebrospinal fluid may differentiate healthy subjects from PD patients (Trupp et al., 2014).

Additional studies showed a decrease in specific neurotransmitters as potential PD markers (Goldstein et al., 2008; Goldstein et al., 2012; LeWitt et al., 2011). The involvement of excitotoxicity and oxidative stress has also been examined in some studies but with inconsistent results (Willkommen et al., 2018; Trist, Hare and Double, 2019).

5.3. Neuroimaging Biomarkers

Neuroimaging methods have become a mature biomarker for the nigrostriatal neurodegeneration. Several research efforts have been expended to develop measures to quantify nigrostriatal neurons by evaluating the potential structure, ultrastructural, or perfusion pattern changes in PD. The most direct approach has been to try to quantify presynaptic nigrostriatal dopaminergic neurons (He et al., 2018).

Neuroimaging tools can be used to assess the disease progression and to detect early changes in PD patients. Contemporary technology is skilled to detect brains anomalies in PD patients using imaging methods, such as transcranial B-mode sonography (TCS), susceptibility-weighted imaging (SWI), diffusion weighted imaging (DWI) (Chung et al., 2009), positron emission tomography (PET) scan and, single-photon emission computed tomography (SPECT) scan (Emamzadeh and Surguchov, 2018).

However, clinical trials that use neuroimaging tools had been reveling discordant results comparing what is reasonable in clinical measures (Perlmutter, 2009). A study described by the Parkinson Study Group (2004) shows that the levodopa treated group had the most additional loss of striatal uptake of the radiopharmaceutical, which proposes a huger loss of nigrostriatal dopaminergic neurons. Though, the clinical measures of the endpoint were disagreeing with the imaging measures. Some other studies have found similar discordant results (Freed et al., 2001; Whone et al., 2003; Ravina et al., 2005; Lang, et al., 2006, Dorsey et al., 2006;).

5.4. Genetic Biomarkers

Genetics are suggested to have an important influence on susceptibility to PD. Complex interactions between genes and environmental factors may be involved behind the PD causes (Delenclos et al., 2016). It has been reported that the risk of developing PD in individuals with family history is 3 until 4.5 times higher than people without family history reports (Schulte and Gasser, 2011; Noyce et al., 2012).

Genetic factors of the etiology of PD, as the genes in peripheral blood, like the proteins related with disease pathophysiology, are expected to become the candidate biomarkers for the diagnosis of PD and parkinsonian syndromes (Yang et al., 2015). The most usual genetic factors of PD have been identified using genome-wide association studies (GWASs) and up to the present time, 90 independent risk signals have been identified (Nalls et al., 2019; Bandres-Ciga et al., 2020). For instance, genes as *Parkin*, *DJ-1* and *PINK1* are related with autosomal-recessive modes of inheritance, that are associated with typical early-onset PD; genes as *ATP13A2*, *DNAJC6*, *PLA2G6*, *FBOX7* and *SYNJ1* are correlated with atypical forms of juvenile-onset PD and genes as *SNCA*, *LRRK2* and *VPS35* are found to lead to typical autosomal dominant PD (Guo et al., 2015; Shen et al., 2016).

Mutations, duplications and triplication in the *SNCA* gene will lead to high penetrance in PD patients. *SNCA* encodes the α-synuclein and mutations of this gene accounts for more than 1% in the general population (Siddiqui et al., 2016). Furthermore, 5%–10% of PD cases have been reported to have mutations in *GBA* gene. This gene has become the most significant genetic risk factor for PD until now (Riboldi, and Di Fonzo, 2019).

6. Parkinson's Disease New Therapies

Current treatment options for PD are limited to symptomatic measures, predominantly in the form of dopaminergic medications (Grimes et al., 2019) and deep brain stimulation (Liang et al., 2020). Furthermore, none of them are able to slow the progression of disease or improve the disabling non-motor features (Stoker, Torsney and Barker, 2018). Though they can confer significant symptomatic benefit, they also result in troubling adverse effects, which can impair the quality of life of patients (Dy, Limjoco and Jamora, 2020). Moreover, none of these alter the course of disease and some of these non-motor features are even partly driven by current drug treatment (Dy, Limjoco and Jamora, 2020), and thus new therapies are needed.

Currently, there is an interest to identify innovative approaches for restoring striatal dopamine in a targeted and physiological manner, as well as a need to identify managements that are proficient to prevent ongoing neurodegeneration and progression of disease. Several experimental methods are presently being investigated in preclinical studies and clinical trials, and it seems expected that the treatment of PD will meet several changes in the future years (Stoker, Torsney and Barker, 2018).

Available diagnostic criteria for PD are based on clinical features and imaging biomarkers. This feature failure on the identification of pathophysiological pathways, and also on the irregularities that happened in the early stages of PD (Stoker, Torsney and Barker, 2018). Based on these reasons, identifying a successful biomarker depends on the understanding the pathophysiology that underlies the disease. However, the full understanding of PD etiology still remains unknown (Cova and Priori, 2018; Cova and Priori, 2018).

However, a number of innovative treatment approaches are beginning to appear in clinical trials. These innovative treatment approaches include viral gene therapies (Palfi et al., 2014), designed to replace the function of the neurons that have been lost; regenerative treatments in the form of stem cell-derived grafts (Barker and Parmar, 2018) and novel drugs capable to targeting the pathogenic mechanisms of PD, with disease-modifying properties (Paolini, Gaetani and Parnetti, 2020). Heterogeneity in PD could involve specific diagnostic biomarkers for variable PD traits, and accordingly, different markers types (Paolini, Gaetani and Parnetti, 2020).

Furthermore, drug discovery is currently focused on the physiologically relevant cellular models, including primary neurons and stem cells (Liu et al., 2020). The recent discovery of induced Pluripotent Stem (iPS) cell technology presents an opportunity to derive human dopaminergic neurons from patients with sporadic and familial forms of PD (Wang and Loh, 2019).

In parallel, high-content screening platforms, provide a network-based method that can resolve temporal and spatial relationships underlying mechanisms of neurodegeneration and drug perturbations (Antoniou et al., 2020). These emergent tools have the potential to create highly predictive cellular models that can bring a greatly transformation in PD drug discovery and development (Skibinski and Finkbeiner, 2011).

Research Aims, Hypothesis, Outcomes And Measures

Research Aims

The principal aim of this thesis is the description of the landscape of PD therapeutic development programs and critically appraise the causes of compound attrition in the distinct stages of drug development, from phase 1 to phase 4 in Parkinson Disease's studies.

Hypothesis

$H0_1$. There is a high percentage of drug development failures.

$H0_2$. There is a decrease in the number of licensed compounds in the last two decades.

$H0_3$: Failures in drug development are observed in all phases of drug development including late stages;

$H0_4$: Failures are related with non-informative early stage trials.

Outcomes and Measures

The main outcome of this methodology is identifying the reasons for development drug success or failure. For this matter, two types of paths will be compared:

(i) successful paths, that allow drug licensing;

(ii) failure paths, that force the suspension of trial before the final phase of the development program.

To achieve the main outcome, the following methodology is proposed.

Methodology

The research developed on the thesis is sequential analysis of the 1304 PD clinical trials. The methodology comprehends a literature research, the design of trial selection parameters, the data extraction, the data analysis, the creation of the PDCard Database and the statistical analysis.

1. Literature Research

After a first review, it was noted that the World Health Organization - International Clinical Trials Registry Platform (WHO ICTRP) platform, that includes the trials registrations datasets provided by 17 clinical trial registries (Ogino, Takahashi and Sato, 2014), seemed incomplete for the search term "Parkinson" compared to the results that appeared on *clinicaltrials.gov* and in ANZCTR in the same circumstances. For this reason, the research and data extraction were carried out in the following order, ensuring a greater coverage of the results for the same search term:

i. Clinicaltrials.gov;
ii. WHO ICTRP;
iii. ANZCTR.

For that reason, this study uses information from clinical trials relating to Parkinson's disease (PD) that are recorded on the 3 platforms: *clinicaltrials.gov*, World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) and Australian New Zealand Clinical Trials Registry (ANZCTR).

Clinicaltrials.gov is a public website that records ongoing clinical trials of all diseases. The database began in 2000. In 2005, the International Committee of Medical Journal Editors (ICMJE) began to require trial registration in a public database as a condition of publication. This greatly increased the number of registrants on clinicaltrials.gov. Registration is required no later than 21 days after enrollment of the first participant. Clinicaltrials.gov provides reliable data on clinical trials starting from 2007.

Clinicaltrials.gov provides comprehensive information in text form about trials. The description includes trial name, sponsor, name of agent, phase of trial, inclusion and exclusion criteria, primary and secondary outcomes, number of participants, duration of trial, and location of trial sites.

The World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) provides access to a central database containing trial registration data sets. It also provides links to the full original records. Data sets from data providers are updated weekly. Our research included the consultation of the Australian New Zealand Clinical Trials Registry, Chinese Clinical Trial Registry, ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR), ISRCTN, The Netherlands National Trial Register, and Australian New Zealand Clinical Trials Registry (ANZCTR).

The Australian New Zealand Clinical Trials Registry (ANZCTR) is an online public registry of clinical trials created in 2005. The ANZCTR accepts trials for registration from all countries, across all therapy areas and all types of health interventions (including pharmaceuticals, surgical procedures, preventive measures, lifestyle, medical devices, treatment and rehabilitation strategies and complementary therapies). The ANZCTR contributes data to the International Clinical Trials Registry Platform (ICTRP), which was developed by the World Health Organization (WHO).

2. Design Of Trial Selection Parameters

Clinical Trials from phase 1 to phase 4 were accessed, in order to determine the characteristics of clinical trials in PD registered between 2000 and August 2019, using the search term "Parkinson". The study population includes Parkinson's disease patients or healthy volunteers participating in trials in early stages of development programs.

Before study selection, a data extraction form with 37 items was developed, based on the guidelines' checklist for the design and evaluation of clinical trials (Moher et al., 2012; Chan et al., 2013). Henceforth, five domains were analyzed.

The general information domain. General information comprised the variables: title of the trial, trial identification number, date of registration, study starts date, estimated study ends date, study ends date; date of last updated, study duration, study status, study size, phase, funder type, funder name, study location, sponsor.

The drug domain. Drug comprised the variables: intervention name, drug administration, drug action mechanism, pharmacological class, molecular entity, orphan or non-orphan drug, drug and target-related markers.

The methods domain. Methods comprised the variables: primary purpose, primary gold, type of trial design (intervention model), method of randomization (allocation), type of blinding (masking), length of treatment intervention, duration of follow-up, endpoint classification (safety, efficacy, other).

The sample domain. Sample comprised the variables: condition, intervention type, original enrollment, final or actual enrollment, age, gender.

The data analysis domain. Data analysis comprised the variables: primary and secondary outcomes, inclusion and exclusion criteria, biomarkers/target-related markers, drug-related markers;

After study selection, (i) the pharmacological class, (ii) the action mechanism of the drug under study, and (iii) the new identity molecules and orphan drugs were accessed using AdisInsight Database. AdisInsight[1] brings together relevant information on drugs in commercial development, clinical trials and drug safety in an accessible and comprehensive database.

3. Data Extraction

3.1. Trials Selection

Trials selection was done manually by one researcher (JSi) without any extraction software and reviewed by the supervisor.

3.1.1. Clinicaltrial.gov - Data Extraction

The clinical trials were accessed in *clinicaltrials.gov* using the search term "Parkinson" with the following *criteria*.

In time range, results were selected from 01.01.2000 to 30.08.2019. In studies type, intervention studies were selected. In the study phase, only early phase 1, phase 1, phase 2, phase 3 and phase 4 were selected. With these criteria, a total number of 1035 studies were obtained.

[1] AdisInsights, http://adisinsight.springer.com

3.1.2. World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) - Data Extraction

The clinical trials were accessed in WHO ICTRP using the search term "Parkinson" with the following *criteria*.

In time range, results were selected from 01.01.2000 to 30.08.2019. In studies type, intervention studies were selected. In the study phase, only phase 1, phase 2, phase 3 and phase 4 were selected. With these criteria, a total number of 658 studies were obtained. Then the studies that were registered in clinicaltrials.gov were excluded, which led to a total number of 253 studies from WHO ICTRP.

3.1.3. Australian New Zealand Clinical Trials Registry (ANZCTR) - Data Extraction

The clinical trials were accessed in *ANZCTR* using the search term "Parkinson" with the following *criteria*.

In time range, results were selected from 01.01.2000 to 30.08.2019. In studies type, intervention (drug) studies were selected. In the study phase, phase 1, phase 2, phase 3 and phase 4 were selected. With these criteria, a total number of 29 studies were obtained. Then the studies that were registered in *clinicaltrials.gov* and WHO ICTRP were excluded, which led to a total number of 16 studies from *ANZCTR*.

3.1.4. Outcome Of Trials Selection

The results of each database (*clinicaltrials.gov*, WHO ICTRP and ANZCTR) were then manually extracted into an electronic database, totalizing 1304 studies.

3.2. Variable Selection

Variables selection was done manually by one researcher (JSi) without any extraction software and reviewed by the supervisor.

All target compounds with anti-parkinsonian potentials were selected; that is, all compounds that the target indication is Parkinson's disease, even in early stage drugs. Only pharmacological interventions were included in this study.

The other study included variables were the following: pharmacological class, duration of the trial, primary outcome, study design, markers related to the therapeutic target, e.g., neuroimaging markers or markers related to the action of the compound (pharmacodynamic markers, pharmacokinetic markers, target-related or drug-related markers).

In order to optimize the information present in the database accordingly to the thesis objectives and hypothesis, the following inclusion and exclusion criteria were applied.

In the study type variable, interventional studies were included, but observational, basic science, cause and cohort studies were excluded.

In the primary purpose variable, treatment and prevention studies were included, but diagnostic, research, screening and supportive care studies were excluded.

In the intervention type variable, drug, combination product, dietary supplement, and biological (drug associated) studies were included, but behavioral, biological (not drug associated), device, procedure, radiation or genetic studies were excluded.

In the conditions variable and in order to be able to define a set of recognized categorized conditions, the ICD-10 was used. ICD-10 is the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD),

a medical classification list by the World Health Organization. It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases.

G20 is a billable code used to specify a medical diagnosis of Parkinson's disease. The diagnosis code G20 includes the following conditions: Parkinson's disease (Hemiparkinsonism), the Idiopathic Parkinsonism or Parkinson's disease. Moreover, it also refers to paralysis agitans, parkinsonism or Parkinson's disease NOS, or primary parkinsonism or Parkinson's disease.

All clinical trials based on these conditions have been included. Due to an extensive spectrum of diseases-related PD condition under study, the ICD-10 was used to categorize the diseases-related PD condition studies.

Contrastingly, all clinical trials not designed specifically to PD, i.e. on the diagnosis code G20, have been excluded.

In the study status variable, terminated, completed, withdraw, not recruiting and recruiting studies were included, but not yet recruiting studies were excluded.

In the study phases variable, phase 1, phase 2, phase 3 and phase 4 studies were included, but early phase 1 and post-market (observational studies) studies were excluded.

3.2.1. Outcome Of Variables Selection

Conclusively, the final database was obtained using the inclusion and exclusion *criteria* mentioned above, totaling a sum of 613 studies interventional studies of G20 – Parkinson's disease (**Figure 1**).

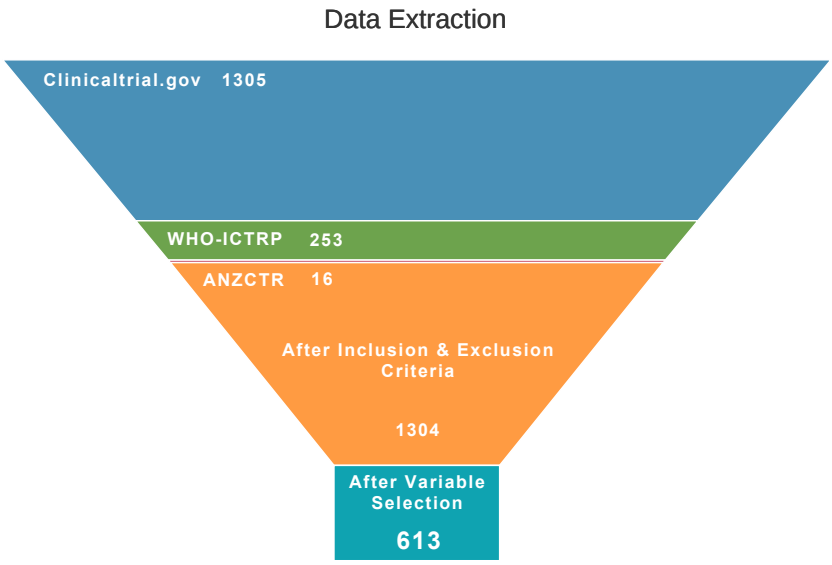


Figure 1. Data Extraction
The sequential strategy of the data extraction is presented.
Three databases were used. Two sets of selection criteria were applied.
Six hundred and thirteen final clinical trials were selected.

4. Data Analysis

The data analysis was obtained by the application of two different methods, in order to answer the thesis principal aim, i.e. descriptive analysis of the landscape of PD therapeutic development programs and hypothesis testing of the causes success and failure rates, from phase 1 to phase 4 in Parkinson Disease's studies.

4.1. Descriptive Analysis Of The Database

To perform the description of the database, the Tableau® data visualization tool was used a bioinformatics tool. This bioinformatic tool was used for data visualization of the database. This bioinformatic tool permitted the variable correlation of the large set of data that comprised the 613 PD studies.

Different studies in PD have been using this bioinformatic tool as for data visualization (Mukherjee, Wu and Jones, 2016; Sharvani, et al., 2020). In this study, Tableau® was used to perform the descriptive analysis and variate correlation presented in the results.

Correlations between the 50 variables were made in order to better detail the information present in the PDCard Database.

4.2. Exploratory Analysis Of Success And Failure Paths

Success and failure rates for each trial phase were calculated by three ways:

(i) the success rate in a trial phase was calculated as the number of compounds that progressed to the next trial phase divided by the number of compounds in that phase;

(ii) the failure rate was the inverse of this;

(iii) the overall failures rate will also be calculated as the ratio between the number of compounds that did not receive regulatory approval and the total number of compounds.

5. PDCard Database

5.1. Database Publication

The final database, an embedded type database, with both (i) trials selection and (ii) variables selection is published in a secured online server : https://tinyurl.com/PDCardDB.

A knowledge discovery method (Pazzani, Mani and Shankle, 1997) with the acquired and stored data was performed. The database was named: PDCard Database, from Parkinson's Disease Card.

PDCard Database characterizes our sample of 613 PD clinical trials.

6. Statistical Analysis

For the descriptive and exploratory analysis, frequency tables (simple/double entries) and boxplots were used as analytical/graphic exploratory tools.

Scale variables were summarized as mean, minimum, maximum and/or other order statistics, when the sample distribution justified it.

Categorical variables were summarized using frequency and percentages.

7. Software

The following pieces of software were used in this thesis.

(i) PUBMED, Google Scholar for the systematic revision of the clinical trials in PDs.

(ii) Tableau® Desktop, V.2020.2, for the statistical/data management and the data exploration/visualization;

(iii) Microsoft Excel, V.16.39, as a spreadsheet platform for clinical trials information management and the PDCard Database generation;

Results and Discussion

Preamble

How was clinical drug development in PD in the last 20 years?

How many studies were registered?

How many studies were completed?

How many drugs were tested?

How many conditions associated with PD was studied?

What was the average length of treatment?

What was the preferred administration drug method?

Were these last 20 years efficient in drug development in PD?

What were the causes for drug development success?

What were the reasons for drug development failure?

What is the compound that received licensing from the regulatory authorities?

How many new molecular entities were licensed?

Who are the main sponsors licensing APIs in PD in the last 20 years?

The results comprehend the data acquired in the (1). PDCard Database, the (2). Descriptive Analysis of the PDCard Database, and the (3). Success vs. Failure Analysis.

The (1). PDCard Database is the knowledge base of the 613 clinical trials, registered between 2000 and August 2019.

The (2). Descriptive Analysis of the PDCard Database is the investigation of those 613 studies addressing the most relevant variables. Fifty variables were analyzed.

The (3). Exploratory Analysis of the Success and Failure Cases in PD Clinical Drug Development is the examination of clinical drug developmental in PD in the last 20 years. It presents the rates and causes of success/failure of the 613 clinical trials and the paths of the 187 tested compounds.

1. PDCard Database

The dataset comprehended the use of 50 independent variables.

The following variables were acquired to compile the knowledge base, in https://tinyurl.com/PDCardDB.

Variables were organized in 3 main categories, based on the SPIRIT guidelines (Chan et al., 2013). Each of the variables was added manually and extracted from the original publication of the clinical trial. Information present in the 3 original databases (clinicaltrials.gov, WHO ICTRP and ANZCTR) was (i) categorized (ii) systemized and

(iii) organized in the following variables. When the information was not present, the original publication of the study was explored in order to complete the database.

1. Administrative Information: from trial design to study status.

2. Participants, Golds and Interventions: from subjects and conditions to drug administration.

3. Data Collection, Management, and Analysis: from API to drug and target-related markers.

A set of 16 derived variables were used in the database to datamining, but not discussed in the descriptive analysis of the PDCard Database. Henceforth, they were added to the database but in annex.

The variables were operated in order to generate and optimize the database. A brief description of the variable and the (i) categorization (ii) systemization and (iii) organization is then presented.

1.1. Administrative Information: From Trial Design To Study Status

Administrative Information included 25 nominal (string) variables. They comprise the following variables.

Source Registry, variable that presents the register of the 3 databases used to extract information.

Title, variable that presents the official title of the clinical trial.

Identification number, variable that presents the official number in the register.

Study type, variable used to filter all the interventional types of study in the 3 databases.

Condition (ICD-10), variable that was used to categorize and filter only PD studies.

Funded by, variable operated in order to separate industry from non-industry studies.

Sponsor/Collaborators, variable containing information from the sponsors.

Location of study, variable operated in order to separate US non-US studies.

Study Phase, variable categorizing the 4 phases of development.

Study Size (Monocenter/Multicenter), variable created in order to separate mono from multicentered studies.

Allocation, variable created only to separate randomized from non-randomized studies.

Trial Design, variable created to individually categorize the type of assignment.

Masking Type, variable created to separate blinded from non-blinded studies.

Masking Characterization, variable created to separate the 4 types of blinding.

Masking Detail, variable created to detail the type of masking used.

Length of Treatment (days), variable calculated individually to present only length of treatment in days.

Study Status, variable extracted directly for the 3 original databases. Includes information about the status of the study (terminated, completed, withdrawn, recruiting, and not recruiting)

Original Enrollment "Target Size", variable manually calculated and individually inserted in the database.

Actual Enrollment, variable extracted from the 3 databases.

Registry Study Date (year), variable extracted from the 3 databases but operated to present only the year of the registry.

Start Study Date (year), variable extracted from the 3 databases but operated to present only the year when the study started.

End Study Date, variable extracted from the 3 databases but operated to present only the year when the study ended.

Estimated End Date, variable extracted from the 3 databases but operated to present only the year when the study is expected to end.

Terminated Study Causes, variable consulted individually from the 613 studies, then inserted manually on the database, and finally categorized to optimize the information presented.

Study Results, variable that was extracted directly from the 3 databases.

1.2. Participants, Golds And Interventions: From Subjects And Conditions To Drug Administration

Participants, Golds and Interventions included 14 nominal (string) variables. They comprise the following variables.

Gender, variable that was extracted directly from the three databases.

Age Distribution (Child, Adult, Older Adult), variable created in order to categorize the age distribution of the subjects. Data was calculated manually and the systemized in three dimensions.

PD Stage, variable created in order to categorize the stage of PD in the study. Data was consulted manually and the systemized in three dimensions (early, middle and advances PD stage).

Healthy Subjects, variable created to separate studies including healthy subjects. Data was consulted individually on each 613 studies.

Conditions: Chapter (CIM 10), Conditions: Diseases, Signs and Symptoms (CIM 10), variable was created in order to organize the diseases, signs and symptoms studied in the clinical trial. The data present in each study was studies, the systematized with CIM 10 classification system, and finally categorized in the different chapters of the CIM 10.

Primary Purpose, variable directly exported from the three databases.

Primary Gold (Safety Vs. Efficacy), variable created in order to only separate safety from efficacy studies. Data was directly extracted from the three databases then systematized.

Primary Gold, variable directly exported from the three databases.

Exploration of the Primary Gold, variable created in order to better describe the primary gold of each 613 studies. Data was manually extracted from the three databases then systematized and categorized.

Intervention type, variable was directly extracted from the three databases.

Drug Administration Route, variable created to define the route of administration. Manually each study was consulted, then information was systematized, and finally several categories were created to optimize the data. Drug Formulation Type, variable created to define the formulation. Manually each study was consulted, then information was systematized, and finally several categories were created to optimize the data.

Drug Administration Type, variable created to define the administration type. Manually each study was consulted, then information was systematized, and finally several categories were created to optimize the data.

1.3. Data Collection, Management, And Analysis: From API To Drug And Target-Related Markers

Data Collection, Management, and Analysis included 11 nominal (string) variables. They comprise the following variables.

Drug (API), variable created to systemize and categorize the active substance of each clinical trial. Data was consulted individually for each study and systemized with https://adisinsight.springer.com (last update on 03.08.2020).

Antiparkinsonian vs. Non-Parkinsonian Drug Class, variable created to separate only the API that is considered an antiparkinsonian drug class, from all the other pharmacological classes. Each study was consulted individually and systemized with https://adisinsight.springer.com.

Principal Drug Modulation Mechanism, variable created to explore the drug mechanism of each 613 clinical trials. Each study was consulted individually and systemized with https://adisinsight.springer.com. Then information was categorized in order to facilitate the clustering of drug mechanism.

New Molecular Entity, variable created to identify the APIs that were new molecular entities. Each study was consulted individually in https://adisinsight.springer.com.

Orphan Drug Status, variable created to identify if the API has an orphan drug status. Each study was consulted individually in https://adisinsight.springer.com.

Principal Drug Modulation Mechanism, variable created to explore the principal mechanism of each of the 187 API in the PDCard Database. Each study was consulted individually and systemized with https://adisinsight.springer.com. Then information was categorized in order to facilitate the clustering of drug mechanism.

Drug and Target Related Markers Study, variable created manually to define if the clinical trial used Drug and Target Related Markers. Each study was consulted individually to complete the database.

Non-Drug Target Related Markers Study, variable created manually to define if the clinical trial used Drug and Target Related Markers. Each study was consulted individually to complete the database.

Biomarkers Class, variable created manually to identify if the clinical trial used a biomarker. Each study was consulted individually to complete the database. Then information was categorized in order to facilitate the clustering the type of biomarker.

Biomarkers Technique Description, variable created manually to explore the biomarker used in the clinical trial, if present. Each study was consulted individually to complete the database. Finally, information was categorized in order to facilitate the clustering the biomarker details.

Target Biomarker Description, variable created manually to describe the target of the biomarker used in the clinical trial, if present. Each study was consulted individually to complete the database. Finally, information was categorized in order to facilitate the clustering the targets.

2. Descriptive Analysis Of The PDCard Database

2.1. Administrative Information: From Trial Design To Study Status

PDCard Database included clinical trials that are only interventional studies (**Figure 2**). In these interventional studies, participants receive some kind of intervention, such as a new drug. The main objective of an intervention study is thus to evaluate the effect of a new drug in a cohort of patients.

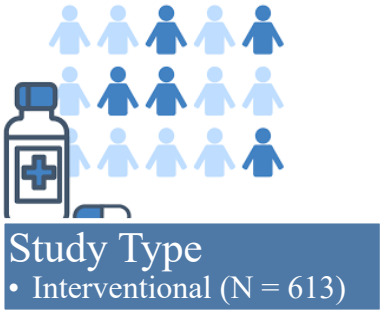


Figure 2. Study Type
Count of interventional type of studies.

All the trials that are included in this study (**Figure 3**)[2] are selected by criteria presented in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).

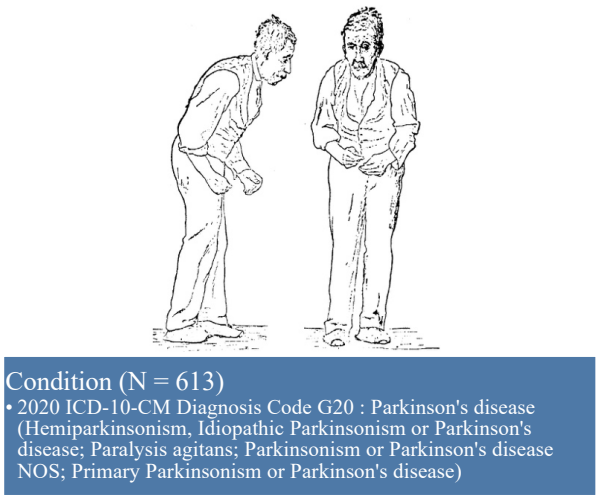


Figure 3. 2020 ICD-10-CM Diagnosis Code G20
Parkinson's Disease

[2] Gowers, W. R. (1887). A manual of diseases of the nervous system. *The Journal of Nervous and Mental Disease*, 14(2), 123-125. (Retrieved at 21.06.2021)

Only the trials with the following conditions are included: Parkinson's disease (Hemiparkinsonism, Idiopathic Parkinsonism or Parkinson's disease); Paralysis agitans; Parkinsonism or Parkinson's disease NOS; Primary Parkinsonism or Parkinson's disease). As mentioned in the methodology, clinical trials were consulted from three separate databases and for later compiling. In **Figure 4** it is shown the number of trials extracted in the source registries, sorted by the study status.

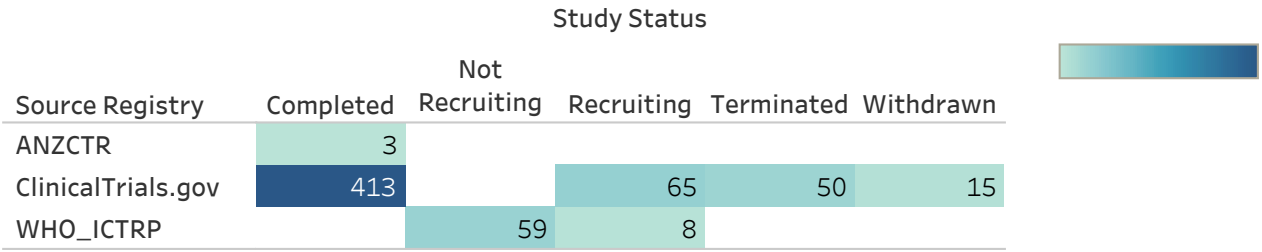


Figure 4. Source Registry (By Study Status)
Count of Source Registry sorted by Study Status. The color shows the count of the source registry.

The studies were mainly present and exported through clinicaltrials.gov, the database that is more comprehensive. Then, the database was completed with the studies provided by WHO_ICTRP and ANZCTR, that were not presented in clinicaltrials.gov. The clinical trials sample is extracted in majority by the clinicaltrials.gov database, totaling 543 studies. These studies comprised 413 completed studies, 65 recruiting studies, 50 terminated studies and 15 withdrawn studies. The WHO_ICTRP then provided 67 clinical trials, 59 not recruiting studies and 8 recruiting studies. The ANZCTR provided 3 completed studies that were not present in the other two databases.

The 613 clinical trials were financed differently. **Figure 5** shows the different types of founders of the clinical trials under study.

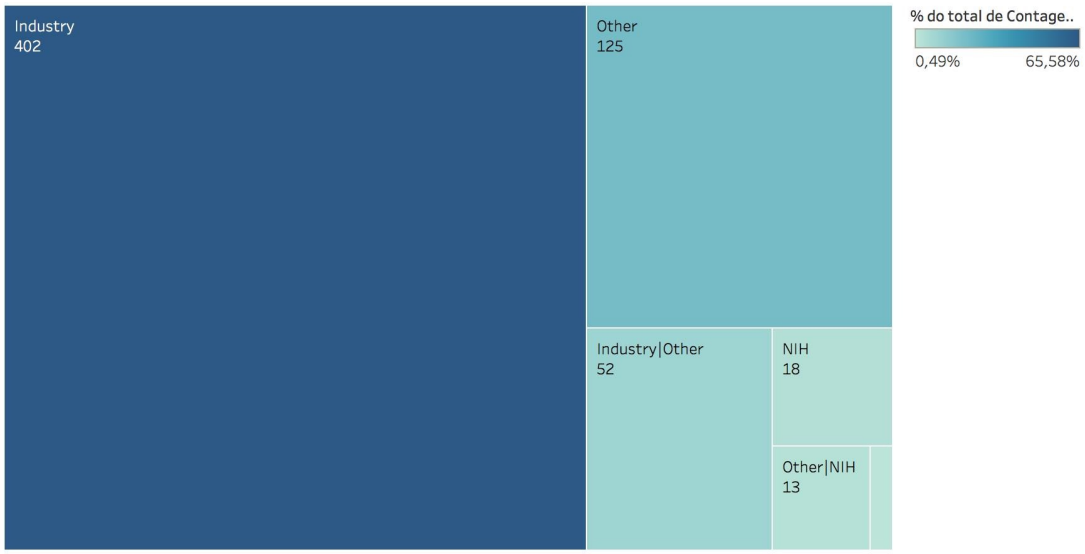


Figure 5. Funded By
Count of funded by. The color shows the % of the variable Funded by.
The size shows the count of the variable Funded by.

The various founders were categorized into: Industry, NIH and Other. The category Other includes the academic medical centers, voluntary groups, and other organizations.

The pharmaceutical companies have funded the majority of the clinical trials (n. = 402). The National Institutes of Health have funded a minority of clinical trials, with 18 studies funded. Other types of funding comprehended 125 studies, plus 52 in cooperation with the industry and 13 with the NIH.

Henceforth, the following circle plot (**Figure 6**) shows the wide sponsorship and collaborators in the 613 studies in PDCard Database.

This image shows the sponsor and collaborators that were most active (more than 10 studies financed). Bial funded 34,67% of all PD studies from 1998 to 2019. UCB Pharma funded 13,33, while Boehringer Ingelbeim funded 12,00%.

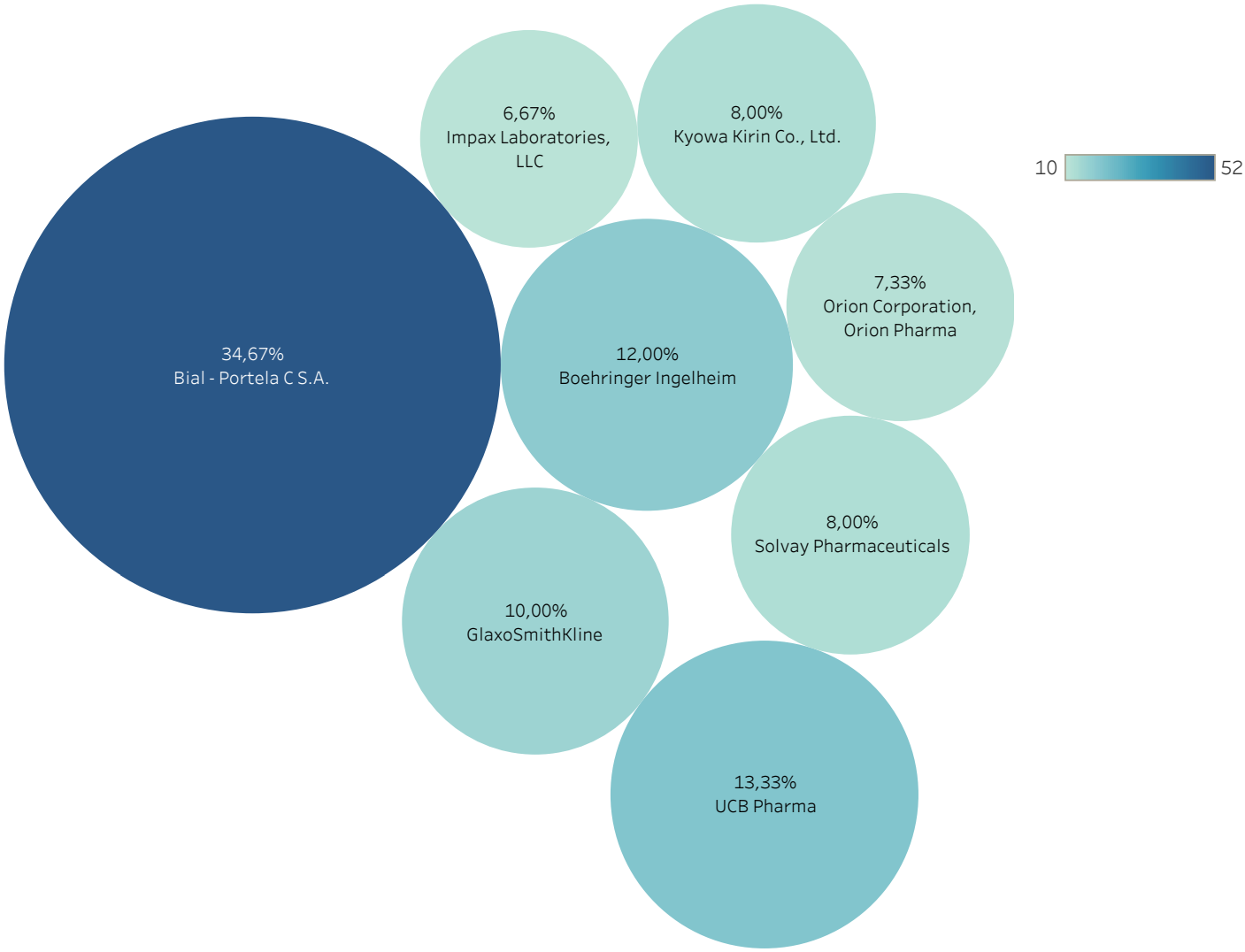


Figure 6. Industry Sponsors And Collaborators Most Active (More Than 10 Studies Financed)
The dimension of the circle is a correspondent to the number of studies financed.
Relative % of all the sponsorship is presented.

Also interesting is to explore the non-industry sponsor and collaborators that were most active (more than 3 studies financed) (**Figure 7**).

NINDS and NIHCC funded 34,88% of all non-industry PD studies from 1998 to 2019. In second, University of South Florida funded 9,30% of all non-industry PD studies from 1998 to 2019.

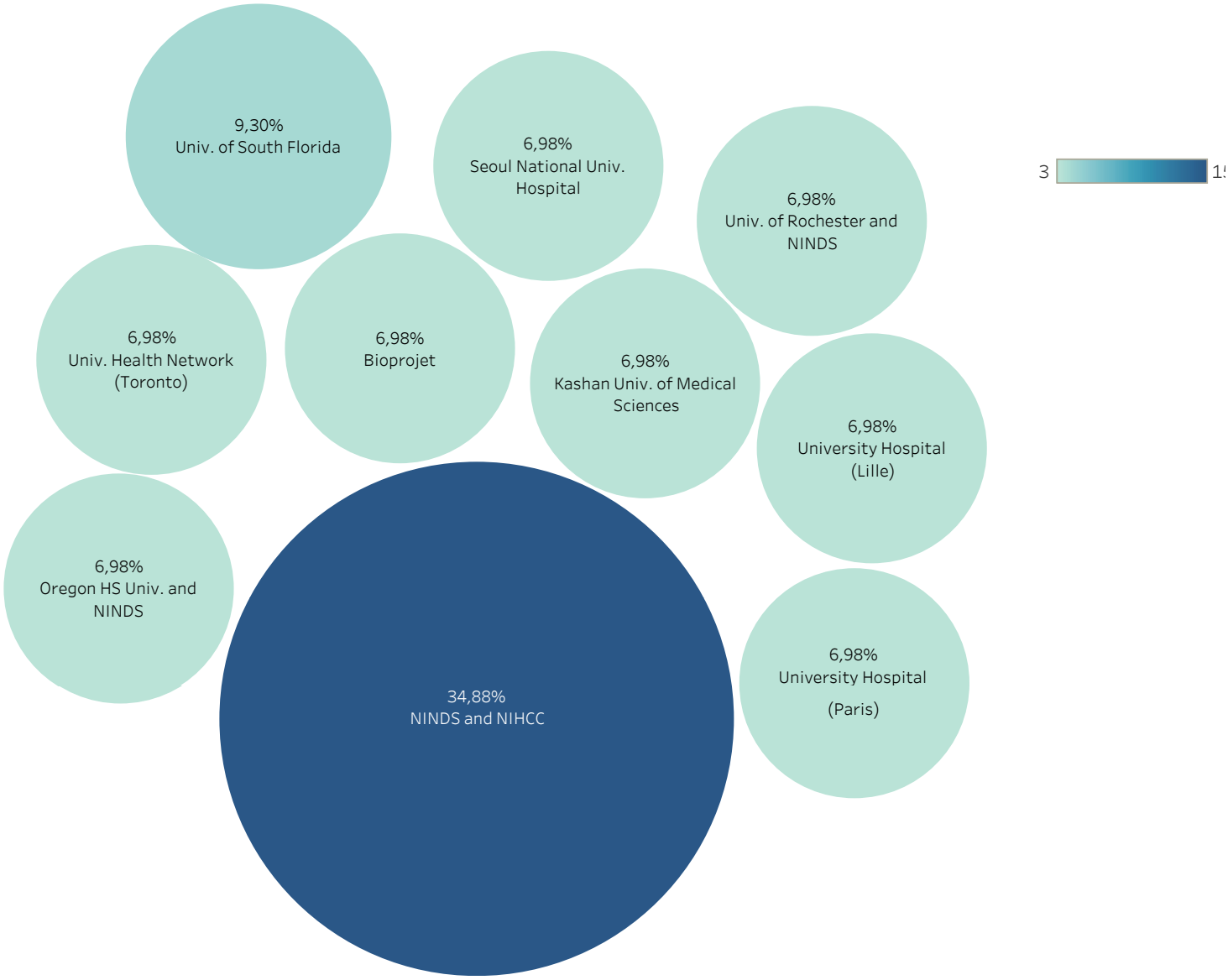


Figure 7. Non- Industry Sponsors And Collaborators Most Active (More Than 3 Studies Financed)
The dimension of the circle is a correspondent to the number of studies financed.
Relative % of all the sponsorship is presented.

That question that then is raised is about the geographical distribution of the studies in the world (**Figure 8**). 296 studies were non-US-based.

One hundred and eighty-four studies were only based in the US.

Ninety-one studies were executed in the US and outsider.

Forty-two studies did not provide their location.

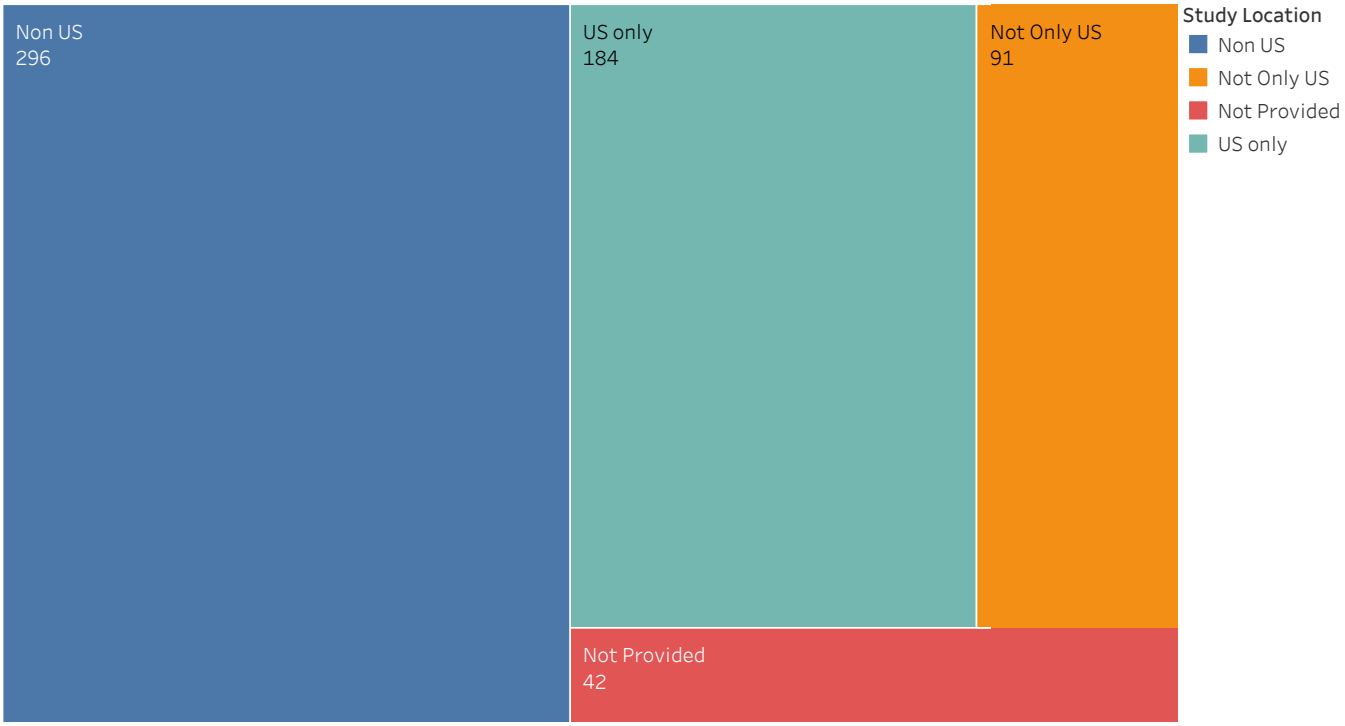


Figure 8. Study Location
Four colors represent the four different geographical distribution.
The size of the squares is a correspondent to the number of studies financed.

After application of the selection criteria, the included interventional clinical were present in different phases of development. **Figure 9** shows the number of the included interventional clinical trials in each phase of development (Phase 1 to Phase 4).

The database includes 115 clinical trials in phase 1, 23 clinical trials in phase 1|2, 194 clinical trials in phase 2, 19 clinical trials in phase 2 and 3, 172 clinical trials in phase 3 and 90 clinical trials in phase 4. Totally they comprise 613 clinical trials.

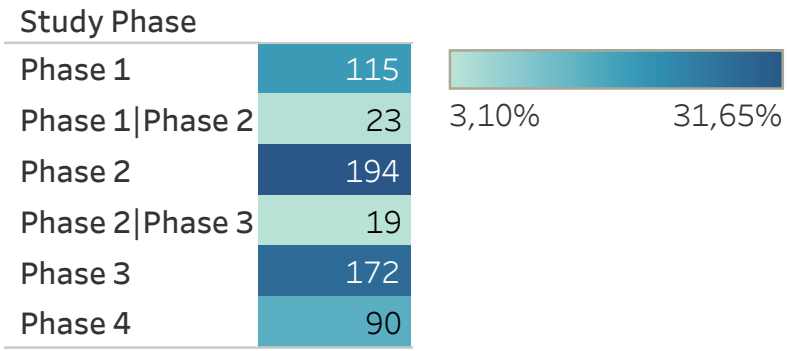


Figure 9. Study Phase
Count of Interventional Studies by Study Phase.
The color shows the % of the total Interventional Studies.

In the last 20 years, studies have been conducted in one site and multiple sites. **Figure 10** shows the overall panorama of the study size of all the studies in the PDCard Database. 42,90% are Multicentered studies, while only 13,38% are monocentered. However, 43,72% are studies that did not provide the study size.

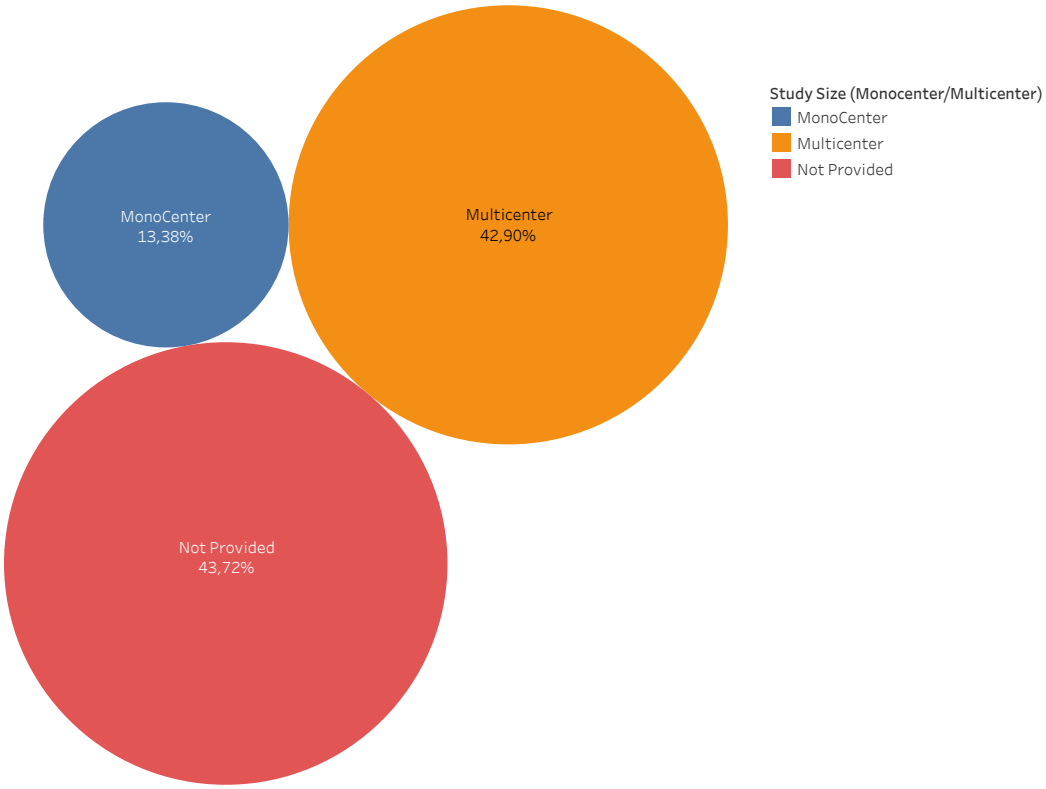


Figure 10. Study Size Categorized By Monocenter And Multicenter Studies
3 colors represent the 3 study sizes.
The dimension of the circle is a correspondent to the relative% of the total trials.

The question that is posted is how study size varies accordingly to the study phase. **Figure 11** shows the study size (monocenter vs multicenter), sorted by study phase. In Phase 1, monocentered design is preferred. In Phase 1|2, Phase 2, Phase 2|3, Phase 3 and Phase 4, multicentered designs are preferred.

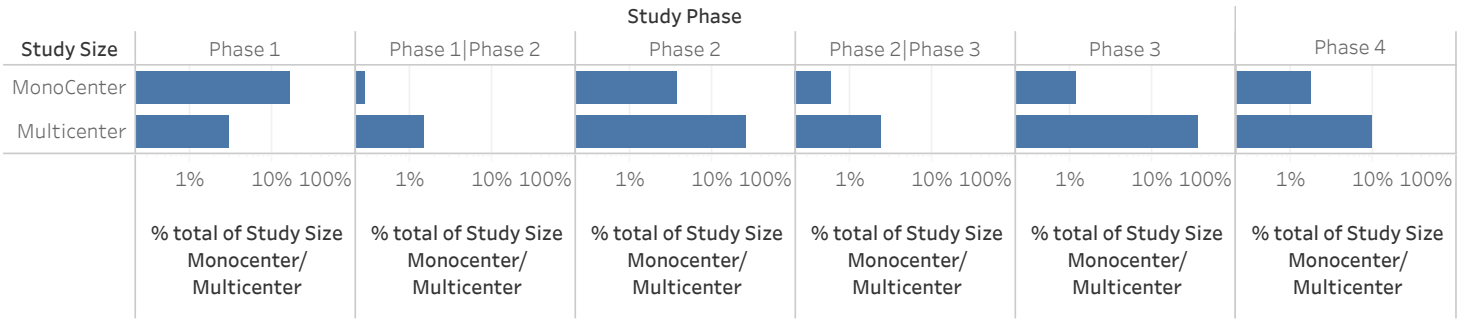


Figure 11. Study Size (Monocenter And Multicenter) Sorted By Study Phase (1-4)
Relative % of the study size is plotted horizontally
on six different study phases.

Similarly, study size (monocenter or multicenter) is dependent on the geographical distribution.

Figure 12 shows thus the study size sorted by the location of the study. Non-US-based studies were the ones that were more monocentered. US-based studies were mainly multicentered.

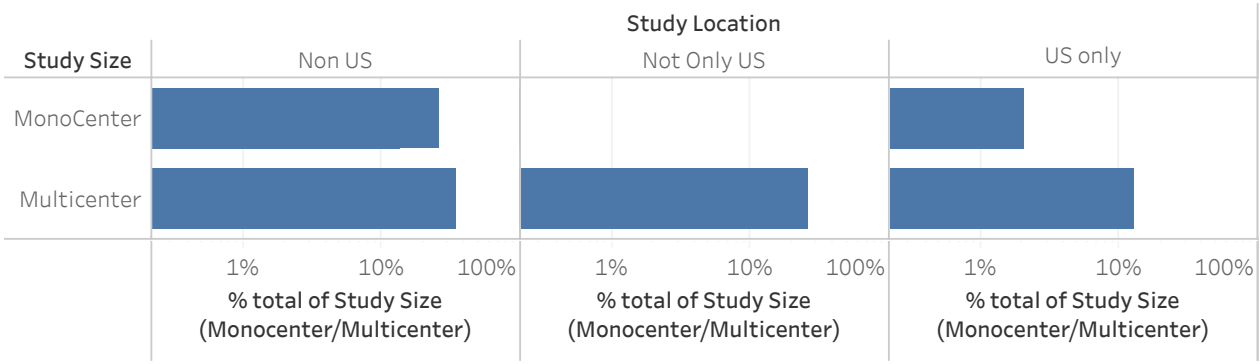


Figure 12. Study Size Sorted By Study Location
Relative % of the study size is plotted horizontally
on three different study locations.

Accordingly, the type of funding also affects the study size. **Figure 13** shows the study size (monocenter or multicenter), sorted by the type of funding.

Industry funded studies were the ones that were more multicentered. Non-industry studies tended to be 50% monocentered and 50% multicentered. NIH studies tend to be multicentered.

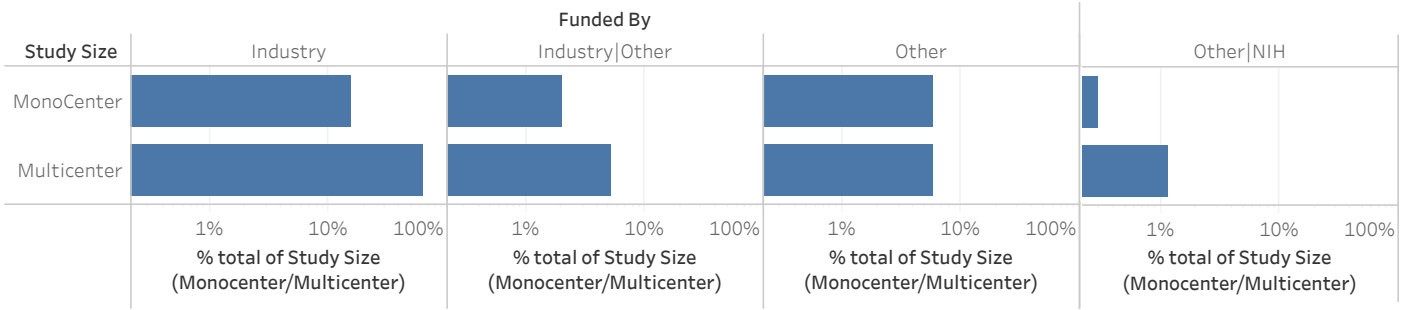


Figure 13. Study Size Sorted By Funding
Relative % of the study size is plotted horizontally
And sorted by 4 different types of funding

The question that is addressed is what type of allocation was used for these 77496 total participants, in the last 20 years of PD drug development. **Figure 14** thus shows the allocation type of the clinical trial study population.

Allocation type were categorized in randomized studies and non-randomized studies.

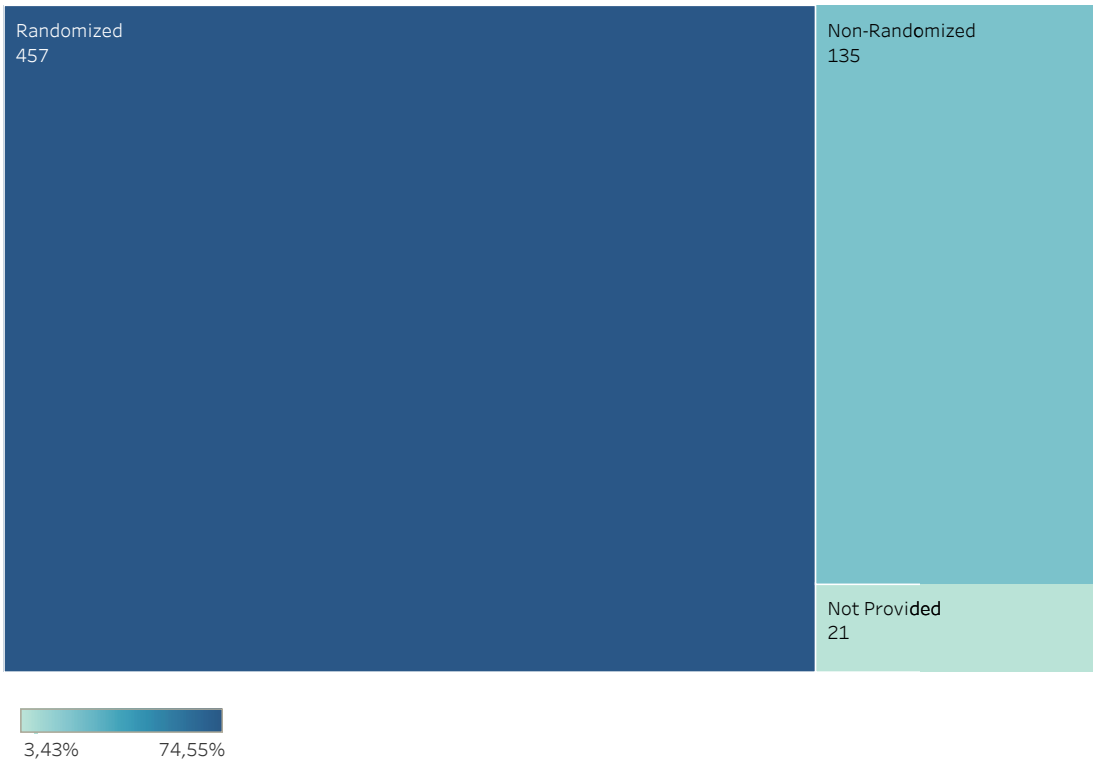


Figure 14. Study Allocation
Color gradation from the darkest to lightest blue represents the higher percentage to a lesser percentage of the type of allocation. The number of studies is presented concomitantly.

From analyzing the figure, it is possible to consider that 457 (74.5%) of the studies were randomized and 135 (22%) are non-randomized studies. Information was not provided for 21 (3,5%) studies.

However, and more detailed, **Figure 15** shows the trials design, but sorted by the study status.

Study Status

Trial Design	Completed	Not Recruiting	Recruiting	Terminated	Withdrawn
Not Provided	18	14	1	2	
Crossover Assignment	87	4	8	10	7
Factorial Assignment	2				
Parallel Assignment	212	34	50	27	4
Sequential Assignment	7		3		
Single Group Assignment	90	7	11	11	4

0,16% 34,58%

Figure 15. Trial Design Sorted By Study Status
Color gradation, from the darkest to lightest blue, represent the number of the largest amount to the least amount, respectively, of trial design use in each type of study status.

Trial design is categorized in crossover assignment, factorial assignment, parallel assignment, sequential assignment and single group assignment.

The parallel assignment design is the predominant model chosen for all study status, except in withdrawn studies. The factorial assignment is the less chosen model for all study status.

Parallelly, in **Figure 16** shows the type of masking used in the last 20 years of PD clinical drug development. This figure shows that 66,72% of the studies are blinded, and that 29,69% are unblinded.

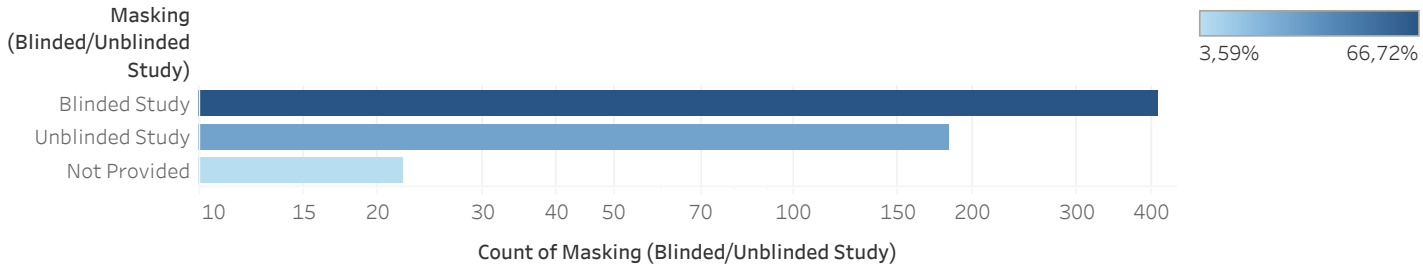


Figure 16. Masking Type
Color gradation, from the darkest to lightest blue, represent the number of the largest amount to the least amount, respectively, of blinded or unblinded studies in the study population.

Moreover, if only the blinded studies are considered (N=409 studies or 66,72%) of the total 613 clinical trials studies, i.e. the unblinded studies (N=182 or 29.69%) and the studies with no data provided on masking (N=22 or 3,59%) are excluded, 5 types of masking were obtained (**Figure 17**). Thus, the masking was categorized in Single, Double, Triple, Quadruple and Open Label.

Double blinded studies (44,99%) were the most used in last 20 years, while the second most used masking was quadruple blinding (39,85%) and principally included the masking between participant, care provider, investigator and outcomes assessor.

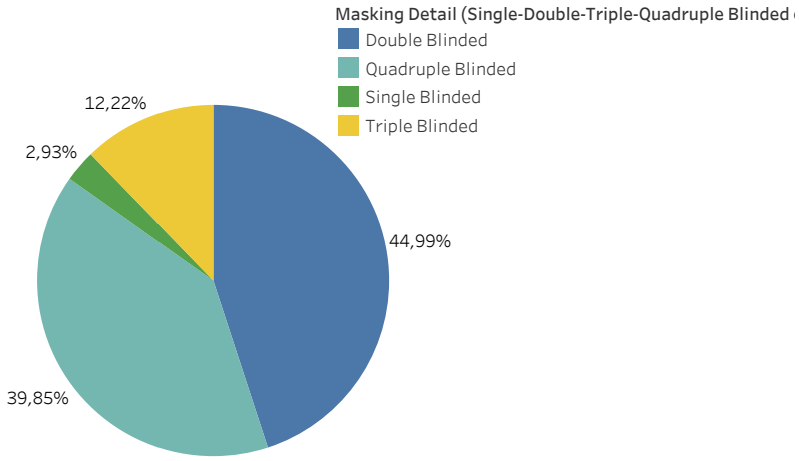


Figure 17. Masking Characterization
The four types of masking are represented by four different colors. % of the total number of studies is indicated in each type.

When a double masking was used, the predominance is between the participant and the investigator of the study.

To better represent the type of masking, **Figure 18** details the 4 types of masking used in PDCard Database.

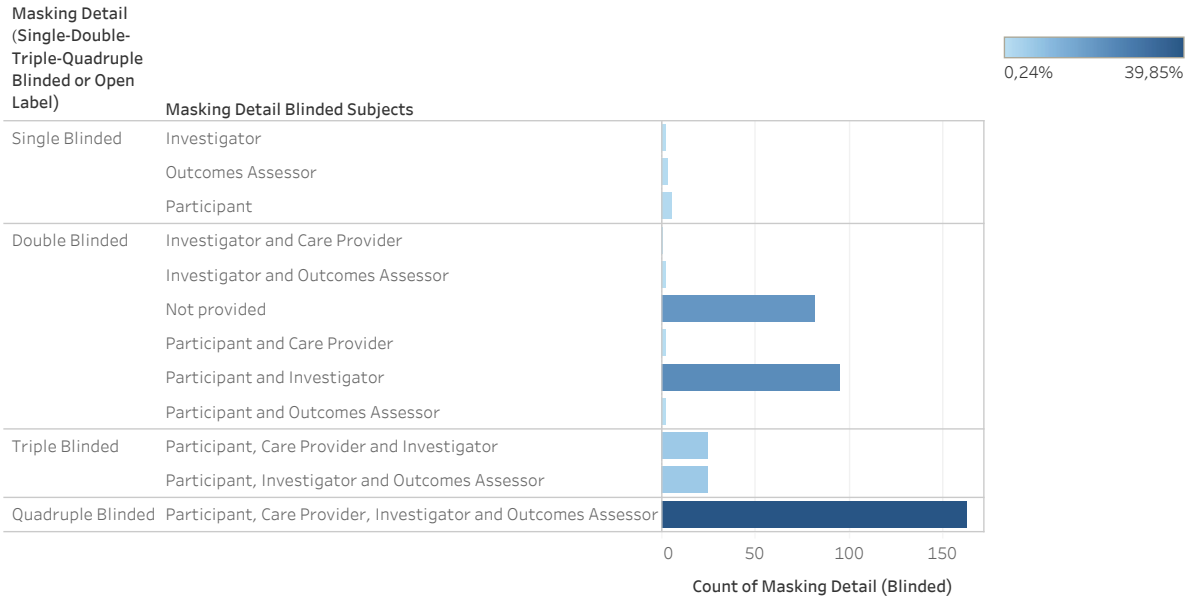


Figure 18. Masking Detail
Number of studies are shown for each type of masking (blinded).

As referred in the introduction, different aspects on the clinical design of the clinical trial may affect its success or failure. One of the aspects is, for instance, the length of treatment.

Figure 19 shows the average days of treatment sorted by study phase.

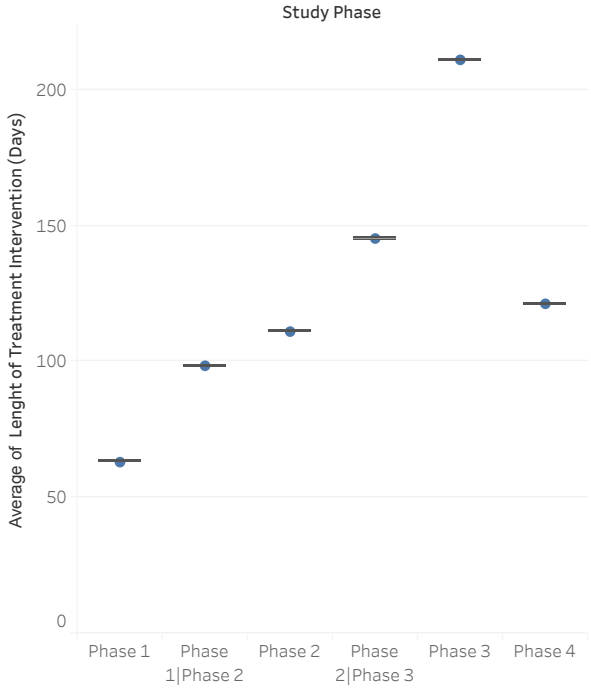


Figure 19. Average Of Length Of Treatment (Days) Sorted By Study Phase
The average length of treatment (in days) is plotted for each study phase for all the 613 studies.

In Phase 1, the average was 63.
In Phase 1|2, the average was 98.
In Phase 2, the average was 110.
In Phase 2|3, the average was 145.
In Phase 3, the average was 211.
In Phase 4, the average was 121.

Also interesting is the perspective of addressing the length of treatment but depending on the primary purpose of the study. **Figure 20** shows the average days of treatment sorted by primary purpose.

Efficacy studies had an average of 110 days.
Safety studies had an average of 165 days.
Safety and Efficacy studies had an average of 134 days.

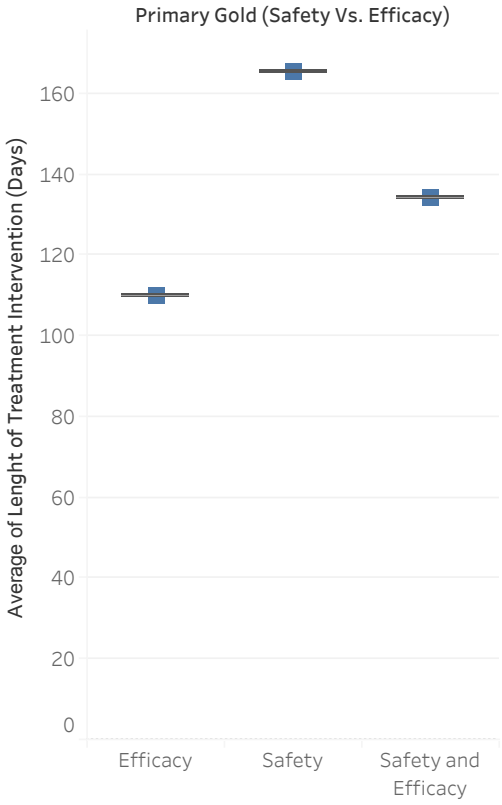


Figure 20. Average Of Length Of Treatment Intervention (Days) Sorted By Primary Gold
The average length of treatment (in days) is plotted for
The 3 main primary golds for all the 613 studies.

One interesting question about trial development is the overall study status of the 613 studies from 1998 to 2019 (**Figure 21).**

67,86% are completed studies, 11,91% are studies in recruiting phase, 9,62% are studies that are not recruiting, 8,16% are terminated studies and 2,45% are withdrawn studies. It is noted that these withdrawn studies are incomplete, but this is not indicative that their development programs are disqualified. Usually, their development programs continue by the establishment of other trials.

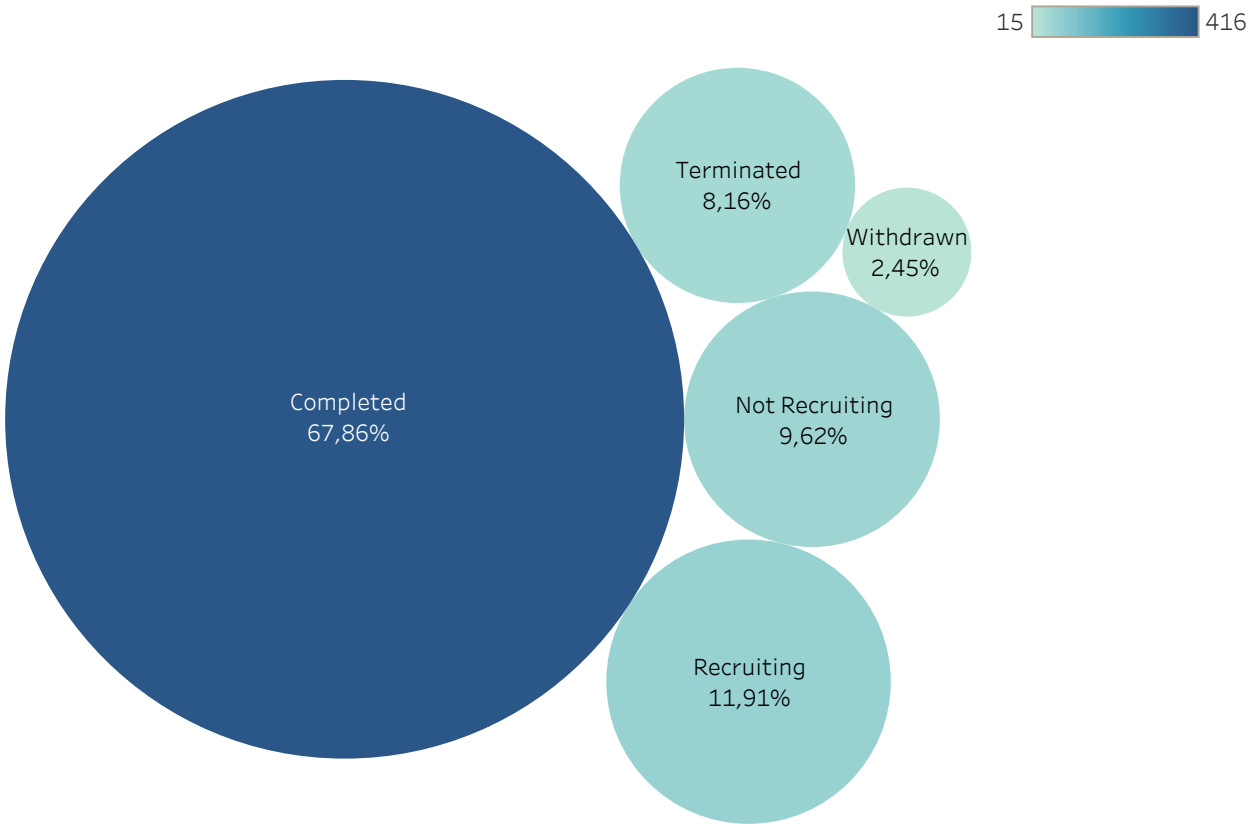


Figure 21. Study Status
The size of the circles is a correspondent to the number of trials.
Relative % of completed, terminated, withdrawn,
not recruiting and recruiting status is presented.

To participate in this treatment and prevention studies, in the last 20 years, several subjects were initially recruited. **Figure 22.A** shows the sum of the original enrollment of each trial before study it started. They were sorted with the actual (year 2019) study status.

The figure shows that the clinical trials that complete the study have expected a high number of participants, as they have a sum of 53774 participants originally enrolled.

Contrastingly, the withdrawn studies were expected rather a low number of participants originally enrolled, i.e. 484.

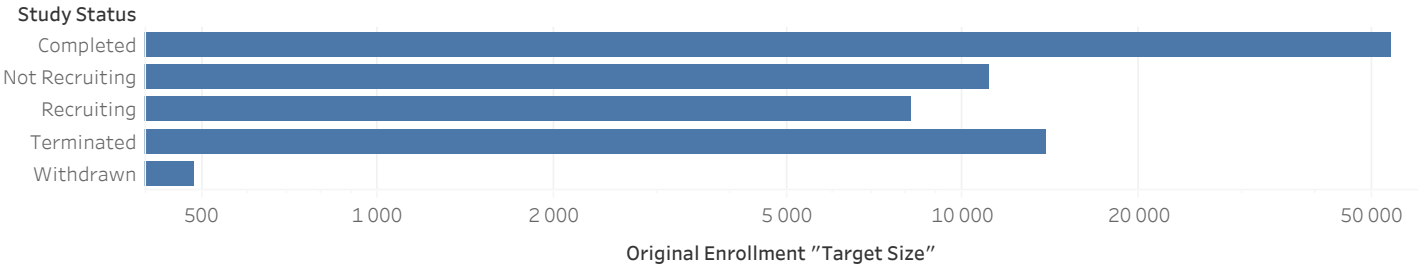


Figure 22.A. Original Enrollment "Target Size"
Sum of total participants originally enrolled,
or expected, for each study status.

Likewise, **Figure 22.B** shows that the clinical trials that complete the study objectives also have a high number of participants, i.e. 58496 actually enrolled.

The terminated studies have a low number of participants, i.e. 11947. Actually enrolled.

The withdrawn studies have no actual participants, as it would be expected.

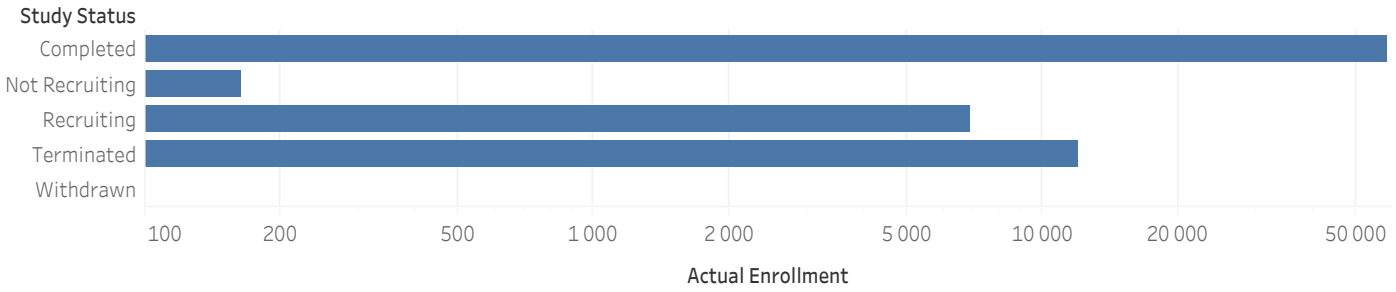


Figure 22.B. Actual Enrollment
Sum of total participants enrolled, for each study status.

One interesting question to pose concerns whether enrollment was higher or lower than expected when the study is RCT is submitted. As shown in **Figure 23**, 85 studies do not provide enough information to calculate whether enrollment was higher or lower than expected.

In 124 studies, enrollment was higher than expected. In this scenario, the expected inclusion of patients in the study was lower than what was actually obtained in the study.

In 187 studies, enrollment was as expected. In this scenario, the forecast was in accordance with reality.

However, in 132 studies, enrollment was lower than expected. In this scenario, the prediction of inclusion of patients in the study was too optimistic when the study was submitted.

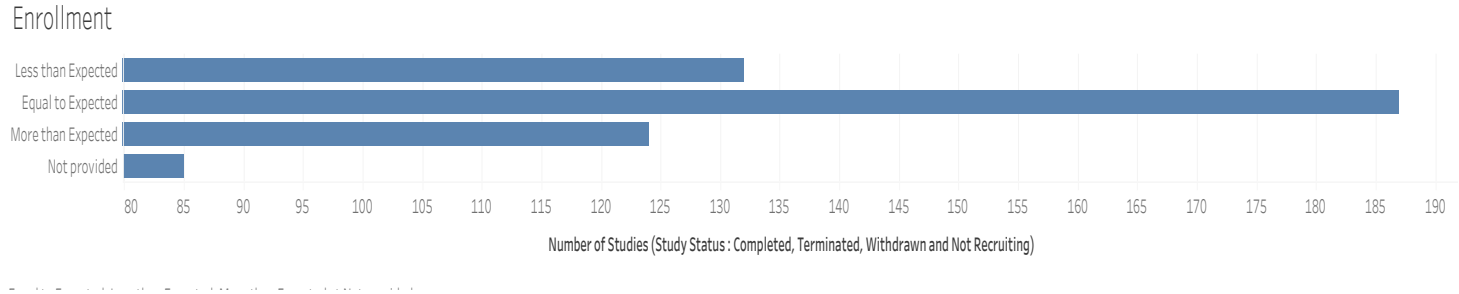


Figure 23. Enrollment By Study Status
The enrollment by the study status (Completed, Terminated, Withdrawn And Not Recruiting) is presented. The total number of studies is presented in the x-axis. The Enrollment (y-axis) was categorized in three groups “Less than Expected”, “Equal to Expected” and “More than Expected”.
The length of the bars represents the quantity of studies in the different categories.

In the last 20 years, the number of API also increased because of the number of registered studies increased.

However, this increase was not in a direct relationship and some registered studies did not produce any API.

Figure 24 shows the study registry date of the studies versus the date of the study start date in each year between 2000 and 2019.

This figure shows that the number of the PD clinical trials registry in the online databases increased significantly since 2005.

Otherwise, the number of PD clinical trials that were started increased significantly from 2015.

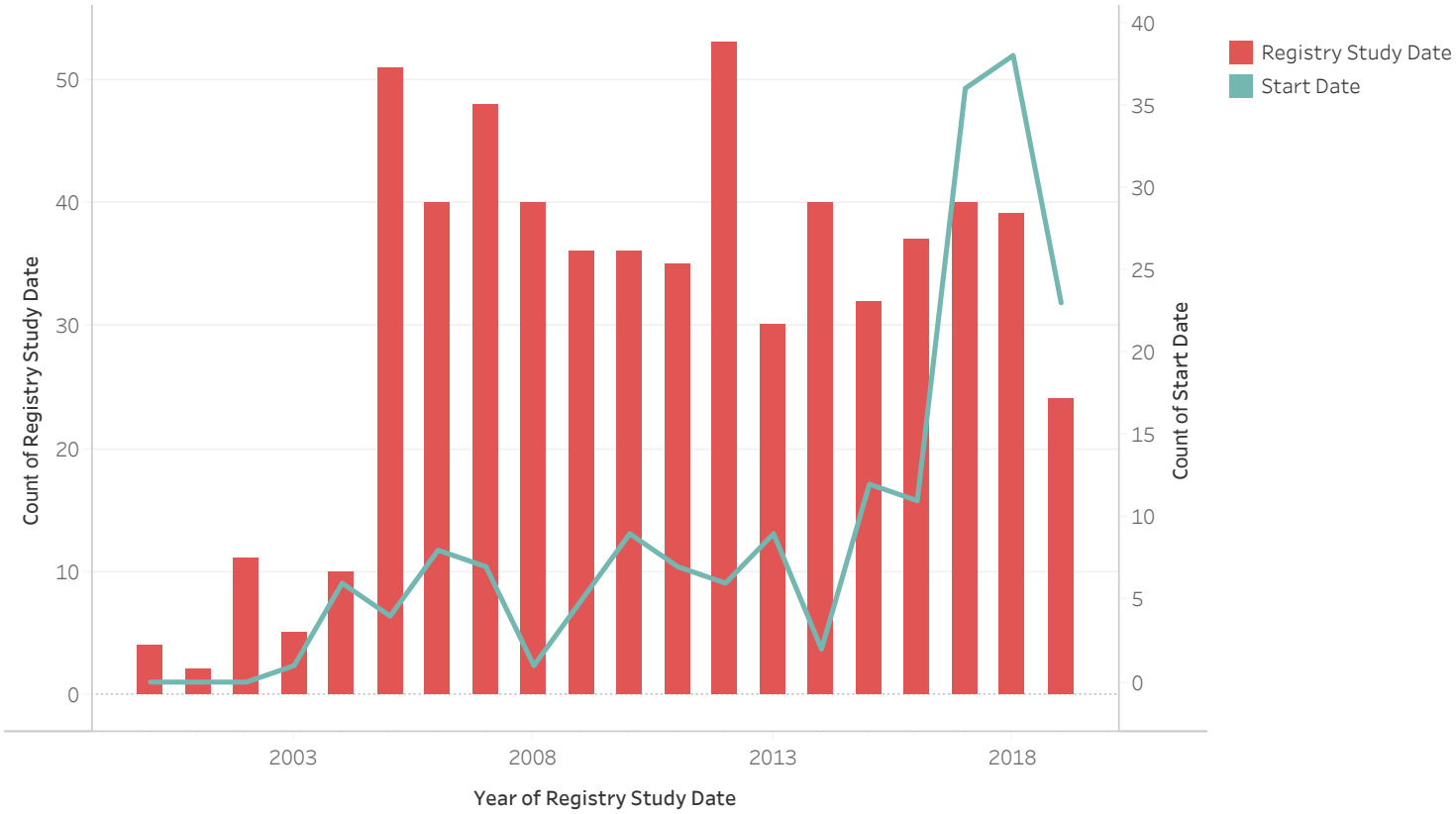


Figure 24. Registry Study Sate Versus Start Study Date
In columns, in red, the year of the registry study date is presented.
The function, in light blue, shows the number of studies that actually started.

Hence, the figure shows an increasing in data update over the years, being higher in the last 5 years. This increase in clinical trials data is due to obligation to registry by the competent authorities on February 29, 2000.

Complementarily, **Figure 25** shows the end study date, not in recruiting status, sorted by study status.

From all the completed studies, the year 2012 was the one with most studies ending (n. = 35).

From all the non-recruiting studies, the year 2009 was the one with most studies ending (n. = 7).

From all the terminated studies, the year 2008 was the one with most studies ending (n. = 12). There were no withdrawn studies before 2007.

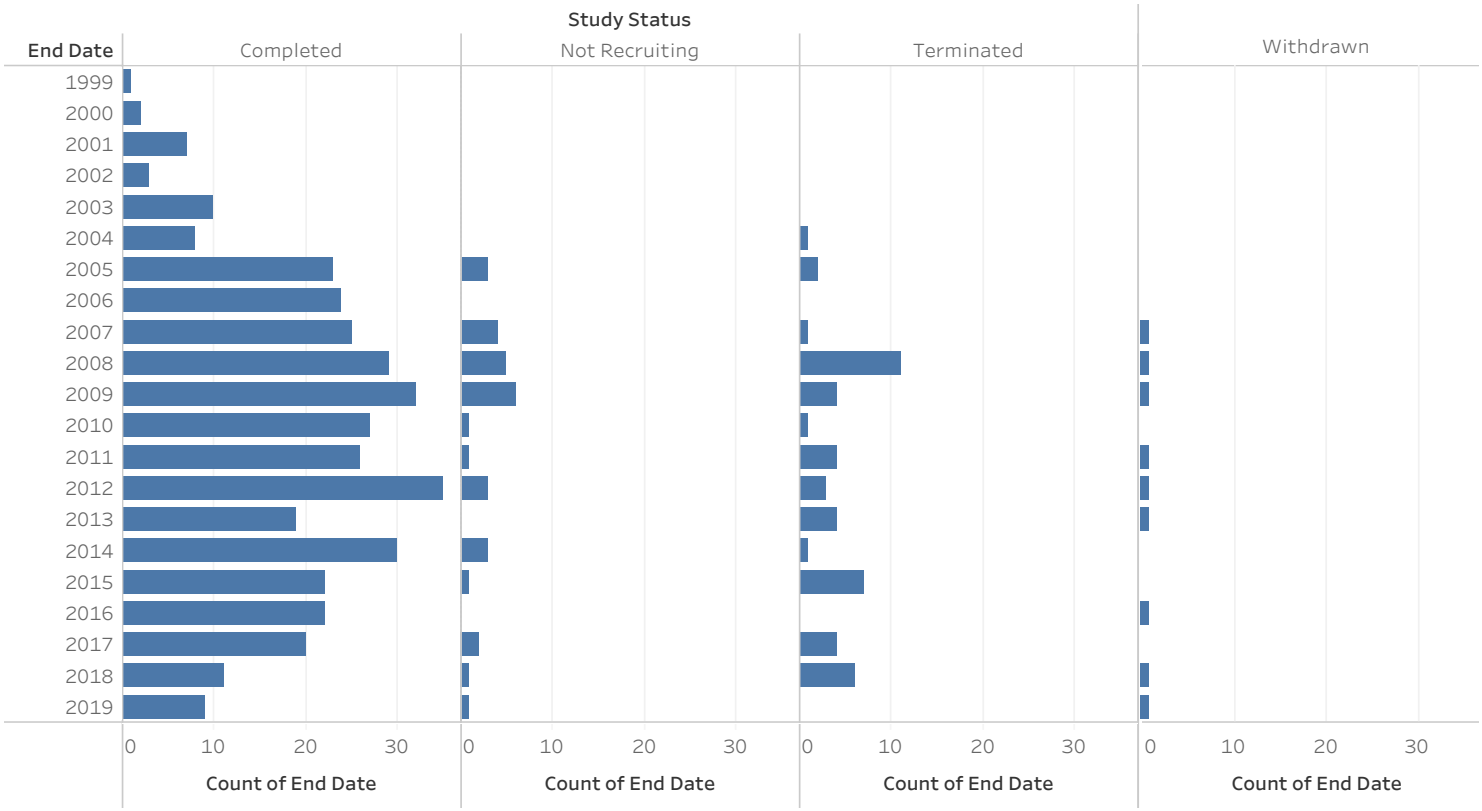


Figure 25. End Study Date Sorted By Study Status (Except Recruiting Status)
The number of trials that ended from 1999 to 2019 is presented.

Supplementary, **Figure 26** shows the estimated end study date, in recruiting status, sorted by study phase.

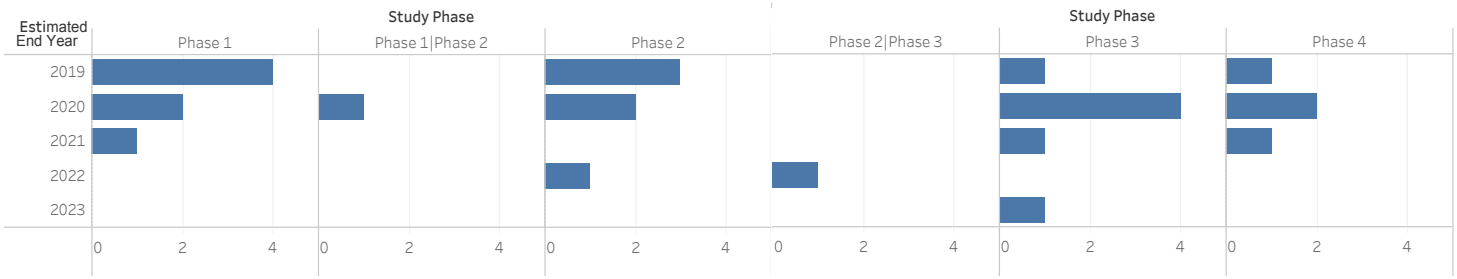


Figure 26. Estimated End Study Date on Recruitment Studies Status sorted by phase of development
The number of trials, in recruitment status,
that are estimated to end from 2019 to 2023 is presented.

In phase 1, 4 studies were planned to end in 2019, 2 in 2020 and 1 in 2021.
In Phase 1|2, 1 study is planned to end in 2020.
In Phase 2, 3 studies were planned to end in 2019, 2 in 2020 and 1 is planned to end in 2022.
In Phase2|3, 1 study is planned to end in 2022.

In Phase 3, 1 study was planned to end in 2019, 4 in 2020, and 1 is planned to end in 2021, and 1 in 2023.

In Phase 4, 1 study was planned to end in 2019, 2 in 2020, and 1 is planned to end in 2021.

What is interesting to notice is that a considerable number of studies were withdrawn or disqualified. **Figure 27** shows the specific causes for withdrawing a specific study.

From all the withdrawn study causes of all studies, in Phase 1|2, 1 study was withdrawn by the sponsor.

In Phase 2, studies were withdrawn because of business reasons, inadequate support to conduct the study, insufficient study materials, site did not obtain LIRB approval, sponsor decided to postpone to after phase 3, study was not funded, or the study group changed.

In Phase 3, the main reason was that a decision to change the study design.

In Phase 4, the main reasons were the following: business decision brand strategy, personnel limitations and intent of pursuing a larger, multi-site study.

Study Phase	Termined Study Causes	
Phase 1	No reasons presented	3
Phase 1|Phase 2	Never initiated. Withdrawn by sponsor	1
Phase 2	Business reasons	1
	Inadequate support to conduct the study	1
	Insufficient study materials	1
	Site did not obtain LIRB approval due to medication usage	1
	Sponsor decided to postpone the performance of this study to after phase 3	1
	Study not funded	1
	The study group changed from patients to a healthy volunteers.	1
Phase 3	Decision to change the study design	1
Phase 4	Business decision brand strategy; no patients enrolled	1
	Study withdrawn due to personnel limitations	1
	Study withdrawn with intent of persuing larger, multi-site study	1

1 3

Figure 27. Causes For Withdrawing A Clinical Trial
Causes are sorted by study phase.

Similarly, what is interesting to notice is that a considerable number of studies was terminated. **Figure 28** shows the specific causes for terminating a specific study.

From all the terminated study causes of all studies, in Phase 1 the most important was first milestone was not met or technical issues with the infusion system.

In Phase 2, lack of efficiency was the primary cause.

In Phase 2|3, the main reason was that it was unlikely to provide evidence of significant effect.

In Phase 3, lack of efficacy and new safety information were the main reasons for terminating the study.

In Phase 4, the main reasons for terminating were insufficient funds, lack, inadequate or insufficient enrollment or payments stopped by grant provider.

Study Phase	Termined Study Causes	
Phase 1	First milestone was not met	1
	Issues with development and supply of infusion system for delivery of IMP	1
Phase 2	Administrative reasons	1
	Difficulty in Recruitment	1
	Due to lack of efficacy in moderate/advanced Parkinson's disease	1
	Due to parent study insufficient efficacy. Not due to safety	1
	Insufficient efficacy. Not due to safety reasons	1
	Lack of efficacy	2
	Lack of recruitment	1
	logistical results found in interim evaluation	1
	No reasons presented	1
	Not enough subjects	1
	Rate of recruitment was very slow	1
	Slow recruitment	1
	Sponsor change - no further support for study. No safety concerns identified	1
	Strategic considerations	1
	Termination of clinical program for Parkinson's Disease	1
Phase 2|Phase 3	Unlikely to provide evidence of significant effect	1
Phase 3	Additional long-term safety data no longer needed	1
	Business reasons	1
	Change in Sponsorship	1
	Company decision to return all rights for other Sponsor	1
	Decision to change the study design	1
	Due to clinical trial supplies shortage	1
	Futility	1
	Lack of efficacy	3
	Lack of efficacy. However, no safety issues were discovered.	1
	Lack of recruitment	1
	Low enrollment	1
	New Safety Information	2
	No reasons presented	3
	Prevalence of H Pylori in the study population was much lower than anticipated	1
Phase 4	Enrollment to slow, insufficient funds	1
	Inadequate enrolment, protocol too challenging for participants	1
	Insufficient patient enrollment, insufficient funds for completion	1
	Lack of recruitment	1
	No reasons presented	5
	Payments stopped by grant provider	1
	Slow enrollment	1
	Slow recruiting	1

1 5

Figure 28. Causes For Terminating A Clinical Trial
Causes are sorted by study phase.

One interesting question to address is if the majority of clinical trials publish their results or not. **Figure 29** shows thus if the study presented results or not but sorted by study Phase.

In Phase 1, 14,2% presented no results, while 4,5% presented results. In Phase 1|2, 3,2% presented no results, while 0,5% presented results. In Phase 2, 25,6% presented no results, while 0,5% presented results. In Phase 2|3, 2,3% presented no results, while 0,8% presented results. In Phase 3, 14,5% presented no results, while 13,5% presented results. In Phase 4, 10,2% presented no results, while 4,4% presented results.

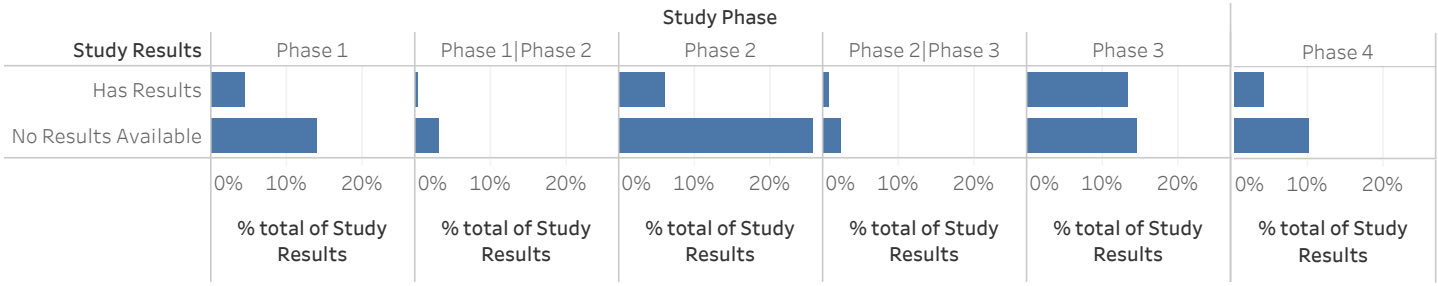


Figure 29. Study Results Sorted By Study Phase
Relative % of the variable results published is plotted horizontally on 6 different study phases.

2.2. Participants, Golds And Interventions: From Subjects And Conditions To Drug Administration

Independently of the PD stage of the disease, PD studies tend to have more male subjects. **Figure 30** shows the gender percentage of the included 613 clinical trials. Most of the clinical trials have no distinction between men and women (92,99%). However, there is a percentage of trials that use only men for their studies, 4,40%.

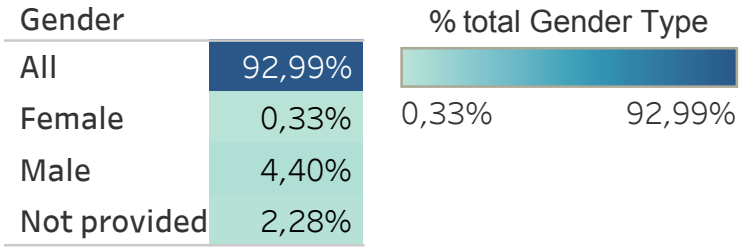
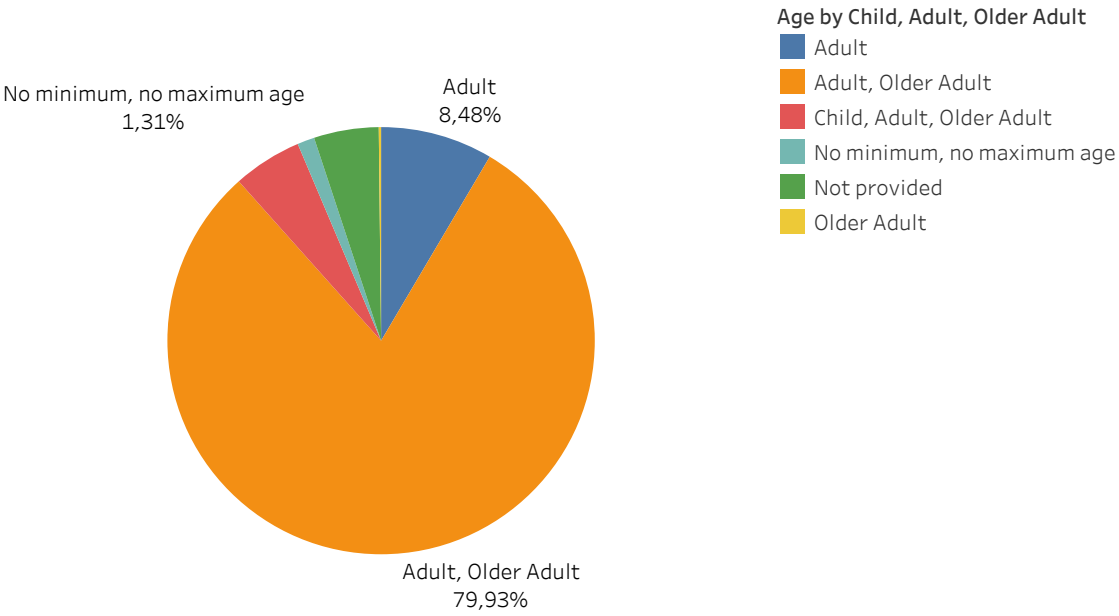


Figure 30. Gender Type
The shades of blue, from the darkest color to the lightest color, represent the percentage of the largest amount to the least amount of gender types considered in the total number of trials, respectively.

Independently of the PD stage of the disease, PD studies tend to have older subjects. **Figure 31** shows the age distribution in the study population that are considered in the 613 studies.

The majority of the studies have recruited adult or older adult subjects, 79,93%. Only 8,48% of the studies included adult subjects, younger than 65 years old. Otherwise, 1,31% of the studies did not mention any age range.



Age by Child, Adult, Older Adult	Count of Age Distribution
Child, Adult, Older Adult	32
Adult, Older Adult	490
Older Adult	1
Adult	52
No minimum, no maximum age	8
Not provided	30

Count of Age Distribution: 1 — 490

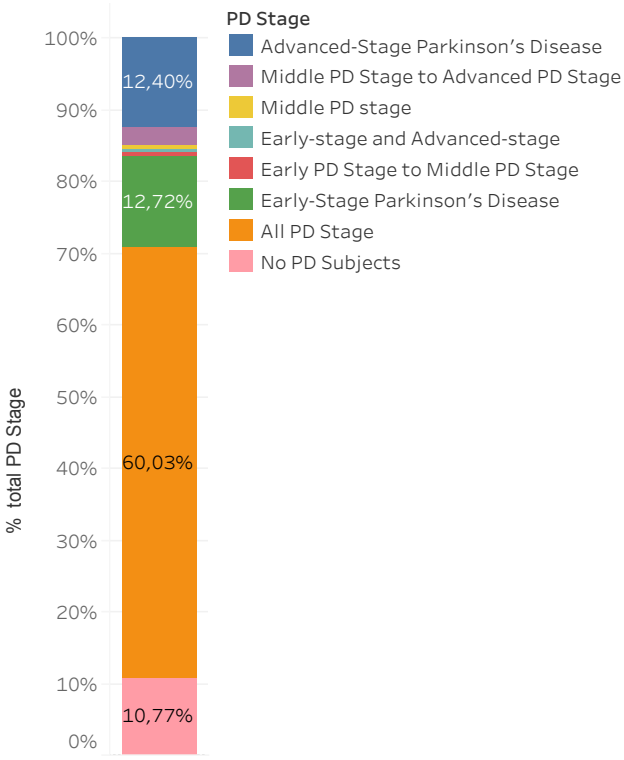
Figure 31. Age Distribution
Aged by child, adult and older adult. % of the age distribution.
The color shows the different age categories.
The shades of blue on the table show the number of studies per age.
The size shows the total %.

In this study the objective was to gather studies that were representative of PD population. In order to adequately show the stage of PD in the last 20 years, **Figure 32** shows the study population stage that is presented in the 613 considered studies. The majority of the studies were considered all Parkinson Disease Stages, without restrictions. This represents 60.03% of the trials.

Otherwise, 12,72% of clinical trials studies are considering only PD subjects in Early-Stage. 12,40 % of clinical trials studies are considered only PD subjects in Advance-Stage. Only 10.77% of clinical trials studies included healthy subjects.

Subjects with Middle Stage to Advanced-Stage Parkinson Disease, 2,61%, were recruited. Fewer subjects with Early Stage to Advanced-Stage Parkinson Disease, 0,49%, were recruited.

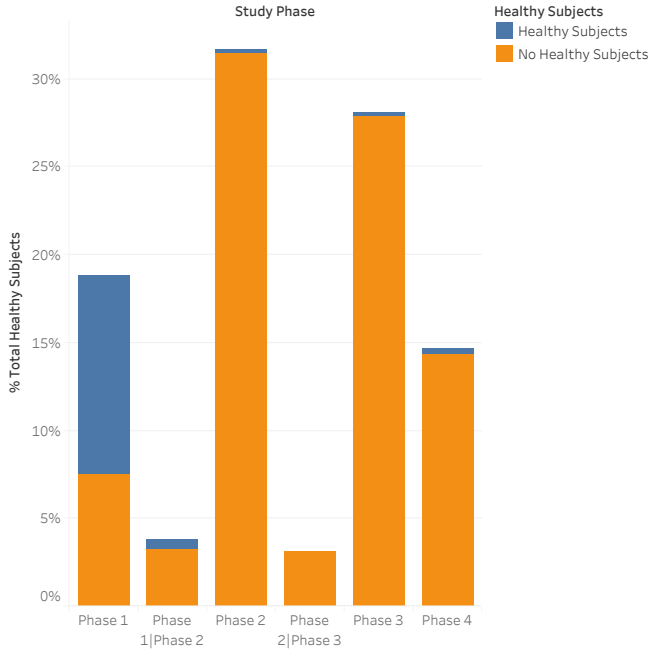
Subjects with Early to Middle-Stage, 0.65%, were almost not recruited. Finally, only 0.32% studies recruited subjects with Middle Stage Parkinson Disease.



PD Stages	% total PD Stage
All PD Stage	60,03%
Early-Stage Parkinson's Disease	12,72%
Advanced-Stage Parkinson's Disease	12,40%
No PD Subjects	10,77%
Middle PD Stage to Advanced PD Stage	2,61%
Early PD Stage to Middle PD Stage	0,65%
Early-stage and Advanced-stage	0,49%
Middle PD stage	0,33%

Figure 32. PD Stage
The y-axis shows the % of total PD Stage. The color shows the different PD stages.

Moreover, it is interesting to notice that few healthy subjects were used in the sample of 613 clinical trials **(Figure 33)**.



Study Phase	Healthy Subjects	% Healthy Subjects
Phase 1	No Healthy Subjects	7,50%
Phase 1	Healthy Subjects	11,26%
Phase 1| Phase 2	No Healthy Subjects	3,26%
Phase 1| Phase 2	Healthy Subjects	0,49%
Phase 2	No Healthy Subjects	31,48%
Phase 2	Healthy Subjects	0,16%
Phase 2| Phase 3	No Healthy Subjects	3,10%
Phase 3	No Healthy Subjects	27,90%
Phase 3	Healthy Subjects	0,16%
Phase 4	No Healthy Subjects	14,36%
Phase 4	Healthy Subjects	0,33%

Figure 33. Healthy Subjects By Study Phase
On the graph, the blue color shows the percentage of Healthy Subjects present in each phase of development. Orange color shows the opposite. The table shows the percentage of each column on the graph.

Figure 33 shows thus the percentage of the healthy subjects considered in the 4 study phases. The graph demonstrates that only phase 1 clinical trials use a considerable healthy sample of subjects in their studies (11.26%).

The graph also shows that phase 2 and phase 3 clinical trials are mostly realized by PD subjects, with a 31.48% and 27.90% of the total 613 studies respectively.

The PD conditions in study of each clinical trial were categorized using the disease chapter sections of ICD-10-CM. **Figure 34** shows the sections of ICD-10-CM.

In this study, most of the diseases studied in clinical trials are diseases of the nervous system (IV), totaling 265 studies.

Otherwise, 264 of the clinical trials were studying the efficacy and safety of the drug itself, without specifying PD as a condition to the study.

Twenty-nine clinical trials studied a sample of subjects with only a mental and behavioral disorders. Nineteen clinical trials studied a sample of subjects with only disease of the digestive system.

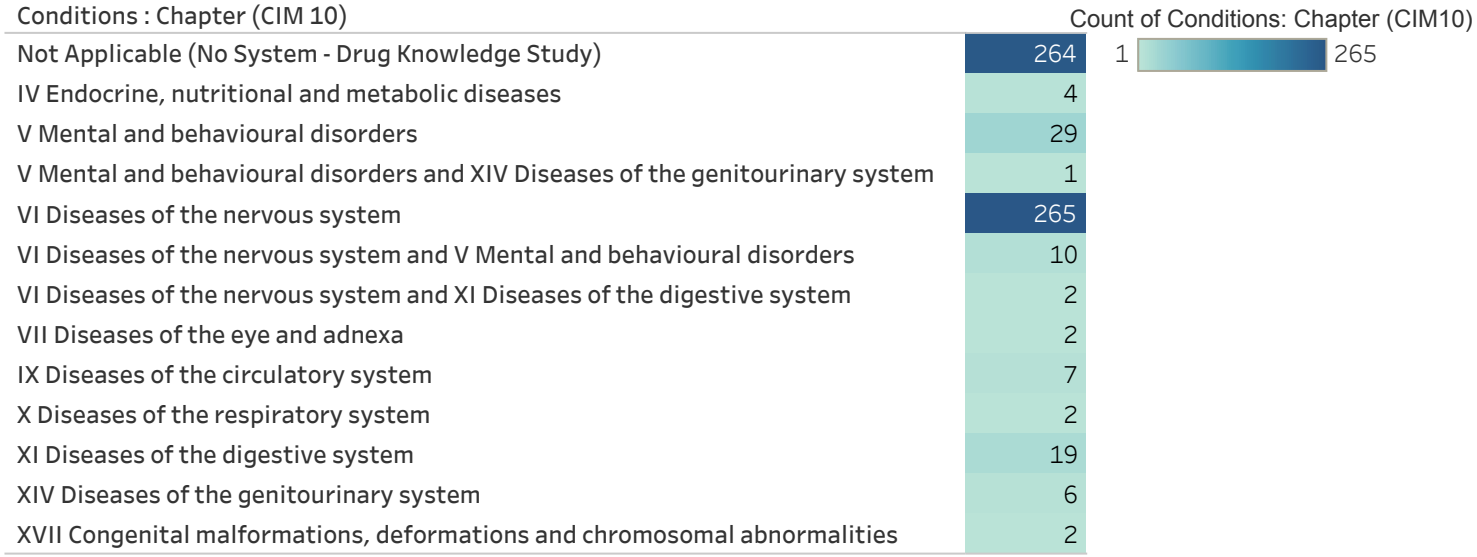


Figure 34. Conditions Distribution By CIM 10 Chapters
The shades of blue, from the darkest color to the lightest color, represent the largest amount to the least number of studies conditions in each chapter of CIM 10, respectively.

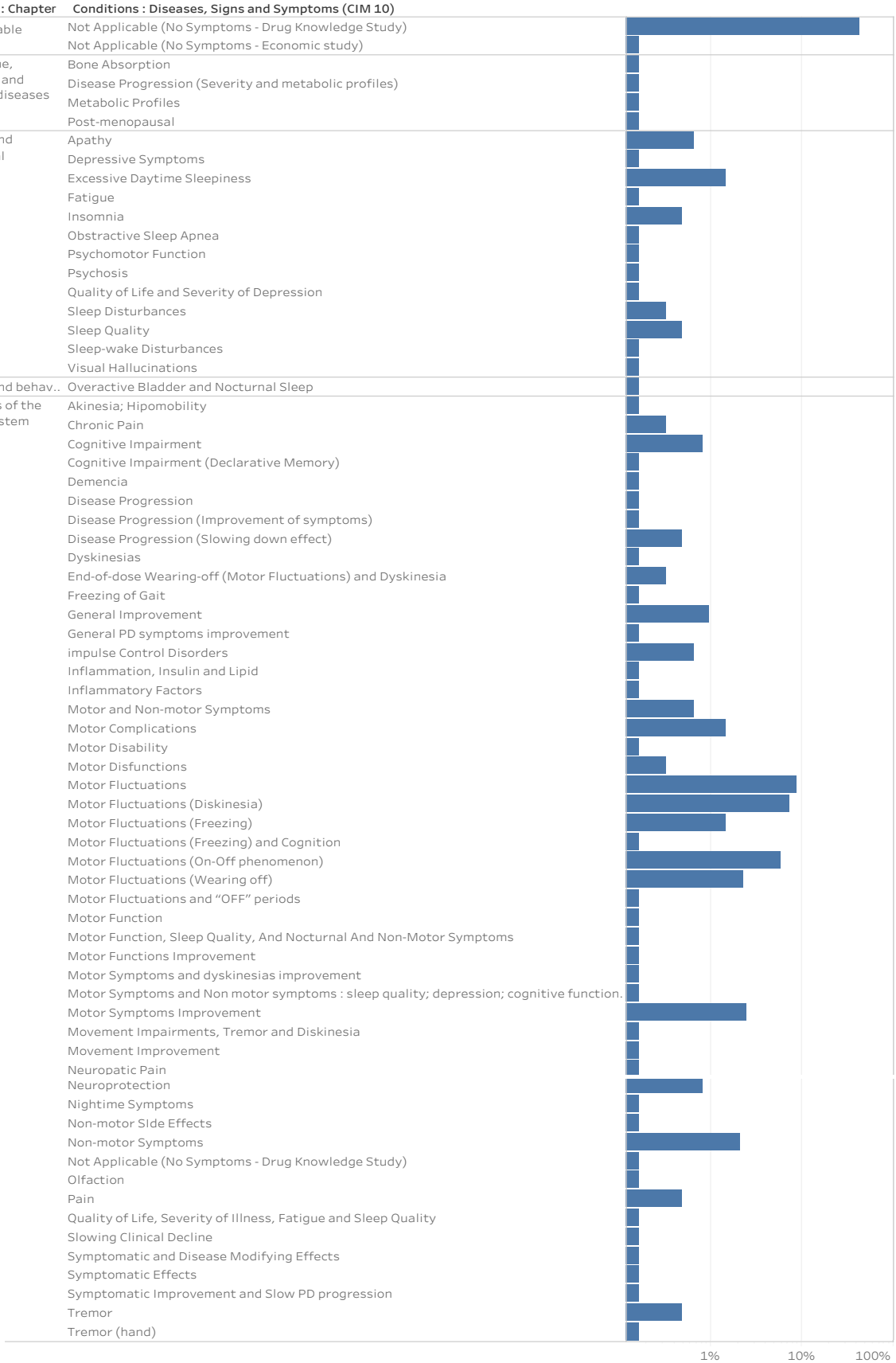
To better understand the specified conditions, **Figure 35** details those conditions (disease, signs or symptoms) in study of each clinical trial. The conditions were categorized by the chapter sections of ICD-10-CM.

Through the graph of **Figure 35**, it can be observed that most studies are drug knowledge studies, i.e. without PD being specified as a condition to the study.

Otherwise, in chapter VI (diseases of the nervous system), there are a high number of the trials that study the improvement of the various types of motor fluctuations 8.81%.

Specifically, neurologic subjects presenting motor fluctuation as dyskinesias comprehended 7.34% of studies. Less but also significantly, studies of the On-Off phenomenon comprised 5.87% of the total 613 clinical trials, and freezing comprised 5.87%, which is also a high number of dedicated trials.

Conditions : Chapter	Conditions : Diseases, Signs and Symptoms (CIM 10)
Not Applicable	Not Applicable (No Symptoms - Drug Knowledge Study)
	Not Applicable (No Symptoms - Economic study)
IV Endocrine, nutritional and metabolic diseases	Bone Absorption
	Disease Progression (Severity and metabolic profiles)
	Metabolic Profiles
	Post-menopausal
V Mental and behavioural disorders	Apathy
	Depressive Symptoms
	Excessive Daytime Sleepiness
	Fatigue
	Insomnia
	Obstractive Sleep Apnea
	Psychomotor Function
	Psychosis
	Quality of Life and Severity of Depression
	Sleep Disturbances
	Sleep Quality
	Sleep-wake Disturbances
	Visual Hallucinations
V Mental and behav..	Overactive Bladder and Nocturnal Sleep
VI Diseases of the nervous system	Akinesia; Hipomobility
	Chronic Pain
	Cognitive Impairment
	Cognitive Impairment (Declarative Memory)
	Demencia
	Disease Progression
	Disease Progression (Improvement of symptoms)
	Disease Progression (Slowing down effect)
	Dyskinesias
	End-of-dose Wearing-off (Motor Fluctuations) and Dyskinesia
	Freezing of Gait
	General Improvement
	General PD symptoms improvement
	impulse Control Disorders
	Inflammation, Insulin and Lipid
	Inflammatory Factors
	Motor and Non-motor Symptoms
	Motor Complications
	Motor Disability
	Motor Disfunctions
	Motor Fluctuations
	Motor Fluctuations (Diskinesia)
	Motor Fluctuations (Freezing)
	Motor Fluctuations (Freezing) and Cognition
	Motor Fluctuations (On-Off phenomenon)
	Motor Fluctuations (Wearing off)
	Motor Fluctuations and “OFF” periods
	Motor Function
	Motor Function, Sleep Quality, And Nocturnal And Non-Motor Symptoms
	Motor Functions Improvement
	Motor Symptoms and dyskinesias improvement
	Motor Symptoms and Non motor symptoms : sleep quality; depression; cognitive function.
	Motor Symptoms Improvement
	Movement Impairments, Tremor and Diskinesia
	Movement Improvement
	Neuropatic Pain
	Neuroprotection
	Nightime Symptoms
	Non-motor SIde Effects
	Non-motor Symptoms
	Not Applicable (No Symptoms - Drug Knowledge Study)
	Olfaction
	Pain
	Quality of Life, Severity of Illness, Fatigue and Sleep Quality
	Slowing Clinical Decline
	Symptomatic and Disease Modifying Effects
	Symptomatic Effects
	Symptomatic Improvement and Slow PD progression
	Tremor
	Tremor (hand)



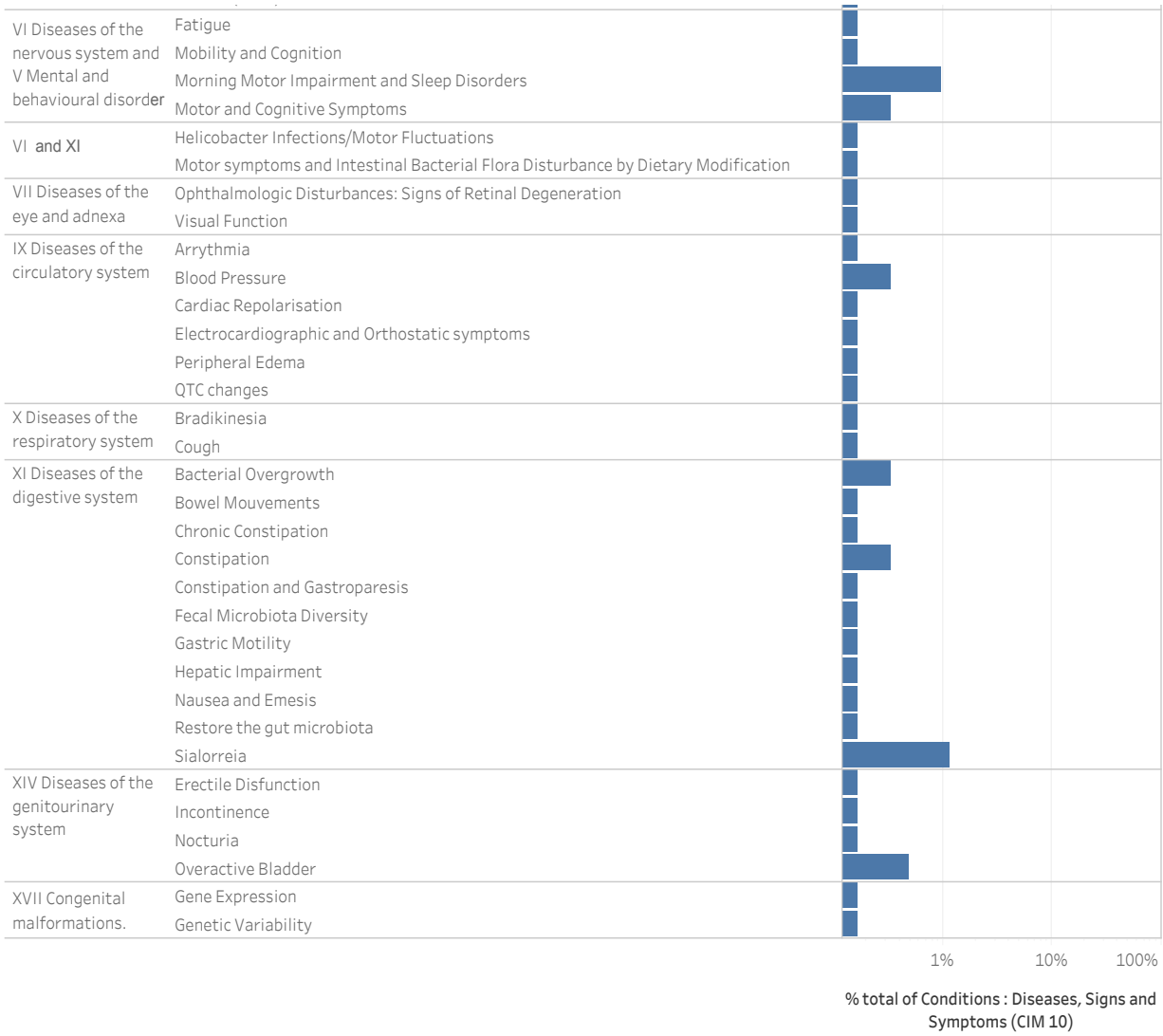


Figure 35. Conditions: Diseases, Signs And Symptoms
Relative % of total PD conditions under study are categorized by the chapter sections of ICD-10-CM.

In chapter V, clinical trials that study the improvement of excessive daytime sleep were the most present, with 1,49%, followed by insomnia (0,49%), and other sleep disturbances (0,33%). Few studies focused on psychotic symptoms induced by parkinsonian medication (0,16%).

In chapter XI, clinical trials focused on sialorrhea were the most present, comprising a total of 1.14% of the studies, followed by constipation (0,33%) and bacterial overgrowth (0,33%).

In chapter XIV, clinical trials focused mainly on overactive bladder, comprising a total of 0,49% of the studies.

The studies present in PDCard Database had only two primary purposes. **Figure 36** shows the primary purpose of the 613 clinical trials, sorted by the study phase. This figure shows that the majority of the trials are designed for treatment purpose. Hence, there are 192 studies only in Phase 2 design for treatment purpose. Being a minority, the prevention studies are mostly located in phase 2, 3 and 4.

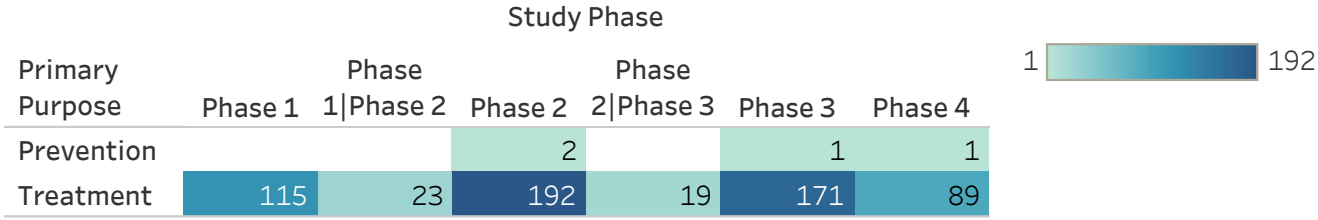


Figure 36. Study Phase
Color gradation from the darkest to lightest blue represents the number of the largest amount to the least amount of Primary Purpose in each phase of development.

As referred in the Introduction the primary gold of the intervention studies are Safety, Efficacy, Safety and Efficacy (**Figure 37**). In this plot, representing the primary gold of the 613 studies, the clinical trials are thus categorized.

The graph shows that 60,03% (368) studies were focused in the drug efficacy, and 15,17% (93) clinical trials were focused in drug safety. Otherwise, the safety and efficacy were revealed as the primary gold on 21,21% (130) clinical trials. Notwithstanding, 3,59% (22) clinical trials do not specify the primary gold of the studies.

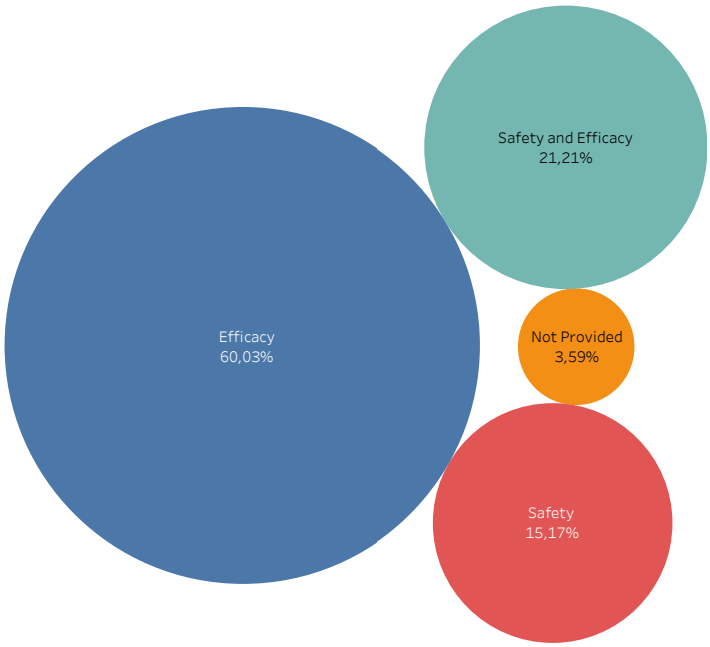


Figure 37. Primary Gold Sorted By Efficacy And Safety
The colors represent each category of the primary gold on the study population. The size of the circles represents the percentage of each primary gold. Higher circles correspond to a high percentage, small circles to low percentage.

To better understand the primary gold of the PDCard Database, the **Figure 38** represents the primary gold of the studies in each phase of the clinical trial development. The graph shows that Efficacy is the predominating gold at all phases of development in the study population. Safety is the second gold designated in all phases, except in phase 4. Tolerability studies were modestly represented and dose finding studies were the least represented in PDCard Database.

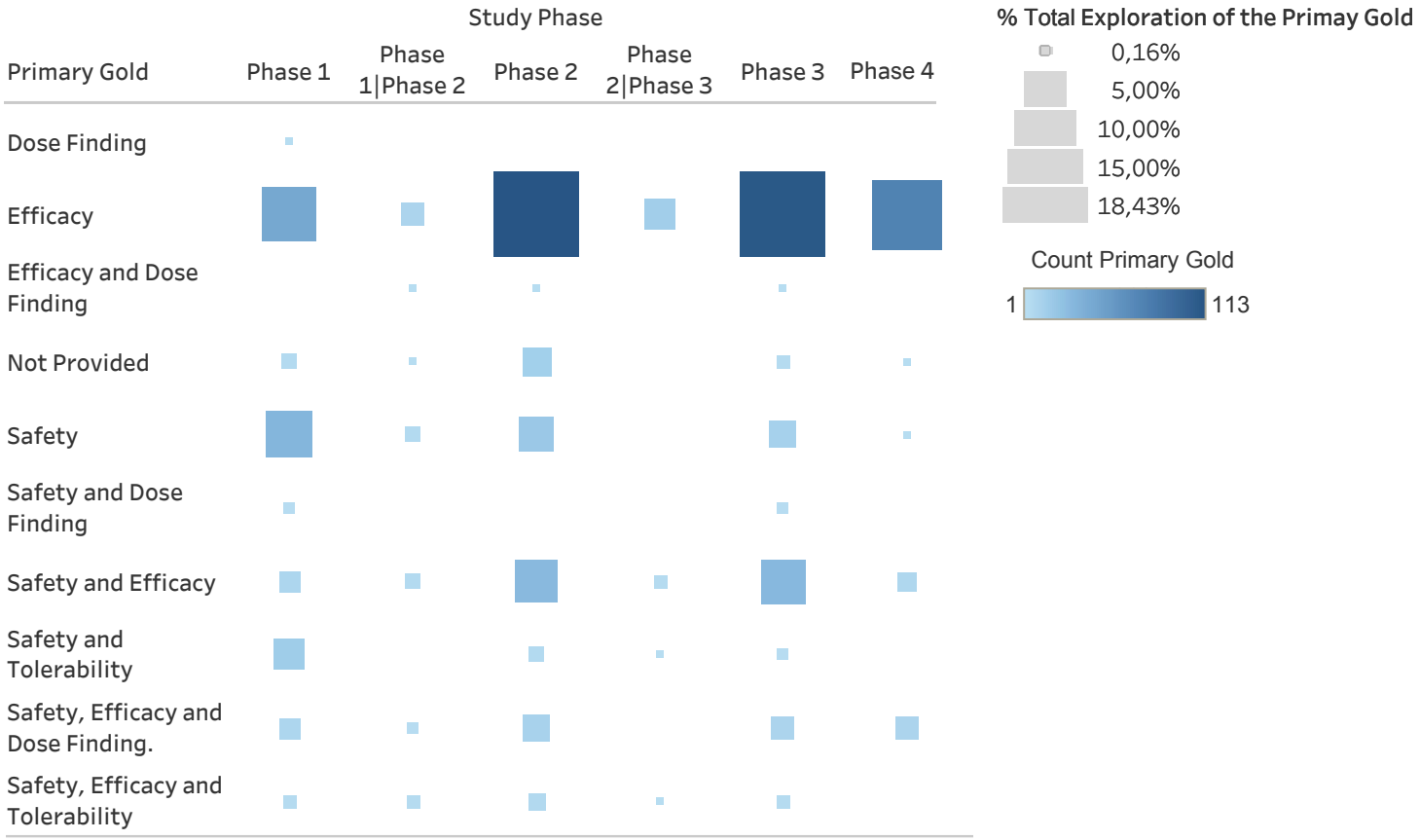


Figure 38. Primary Gold Sorted By Study Phase
Color gradation, from the darkest to lightest blue, represent the number of the largest amount to the least amount of Primary Gold's type in each phase of development.

Also important is to better understand the primary gold of efficacy and safety studies. **Figure 39** explores the primary gold of the studies in each phase of the clinical trial development. As shown in the chart different primary golds are preferred for each study phase of PD drug development.

In the phase 1 the majority primary gold considered by the trials is the evaluation of safety.

In the phase 2 the majority primary gold considered by the trials is the evaluation of effectiveness.

In the phase 3 the majority primary gold considered by the trials is the demonstration of the therapeutic benefit and effectiveness.

In Phase 4 the majority primary gold considered by the trials are not only the optimization of the medication use by evaluation of drug interactions, but also additional adverse effects (pharmacovigilance).

Few studies demonstrate both therapeutic benefit and safety. Lesser studies address the questions of both dose-ranging and short-term security profiles.

Interestingly, the primary gold that is less studies is the pure pharmacokinetic and pharmacodynamic profiling form all the 613 clinical trials.

Figure 39. Primary Gold Detail Sorted By Study Phase
Color gradation from the darkest to lightest blue represents the number of the largest amount to the least amount of Primary Gold's Details in each phase of development.

Complementarily, it is important to note what type of intervention was applied. **Figure 40** shows the different intervention type products that are considered in the 613 clinical trials. The intervention type product used is mostly used is drug type, that totalized 596 of the studies. Of lesser representativeness, the biological and dietary supplements products totalized six and eight of the studies, respectively. Combination products correspond to three studies only.

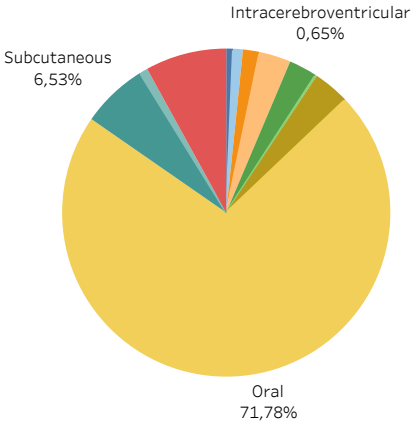
Intervention Type	
Drug	596
Dietary Supplement	8
Biological (Drug)	6
Combination Product	3

% total Intervention Type

0,49% 97,23%

Figure 40. Intervention Type Compounds
The shades of blue, from the darkest color to the lightest color, represent the percentage (right) and the number (left) of the largest amount to the least amount of intervention types considered in the total number of clinical trials, respectively.

In the past years, different types of drug administration in PD have been developed. Despite the new route of administration, oral administration still remains the most tested in PD clinical drug development. **Figure 41** shows the different administration routes utilized in the clinical trial's population.



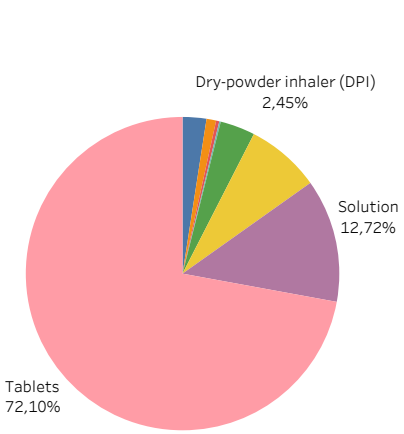
Drug Administration (Choice of Route)
- Intracerebroventricular
- Intraduodenal
- Intramuscular
- Intranasal
- Intravenous
- Not Applicable
- Not Provided
- Oral
- Subcutaneous
- Sublingual
- Transdermal

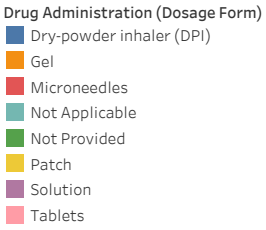
Drug Administration Route	% Drug Route
Oral	71,78%
Transdermal	7,99%
Subcutaneous	6,53%
Not Provided	3,59%
Intranasal	3,10%
Intravenous	2,77%
Intramuscular	1,63%
Intraduodenal	0,98%
Sublingual	0,82%
Intracerebroventricular	0,65%

Figure 41. Drug Administration Route
The different routes of administration are represented by different colors. % of the different routes are presented in the table at the bottom right.

The routes considered are divided in Intracerebroventricular, Intraduodenal, Intramuscular, Intranasal, Intravenous, Oral, Subcutaneous, Sublingual and Transdermal Route. The graph shows a preference for the oral route administration by 71,78% of the studies. Secondly, 7,99% of the studies used the transdermal route for drug administration. Thirdly, the subcutaneous studies have used in 6,53% of the total clinical trials. The Intracerebroventricular route is the less considered, with a utilization for only 0,65% of the studies.

Likewise, different formulations have been developed and in PD drug development. **Figure 42** shows the percentage of the drug formulations presented in the clinical trials studies.



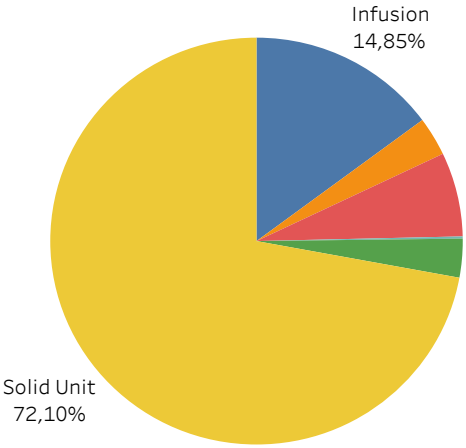


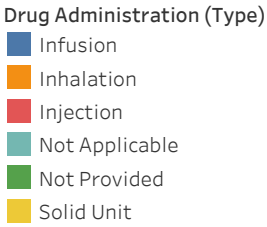
Drug Formulation Type	% Drug Form
Tablets	72,10%
Solution	12,72%
Patch	7,67%
Not Provided	3,59%
Dry-powder inhaler (DPI)	2,45%
Gel	0,98%
Microneedles	0,33%
Not Applicable	0,16%

Figure 42. Drug Formulation Type
The different formulation types are represented by different colors.
% of the different formulation types are presented in the table at the bottom right.

The different formulations considered are tablets, solutions, patches, microneedles, gels and dry-powder inhalers. This figure shows that the majority of clinical trials use tablets formulations (72,10%). The solutions are used in 12,72% of the clinical trials and the dry-power inhaler is used in 2,45% of the studies. The microneedles are the less used, with a percentage of 0.32%.

Comparably, drug development has also improved in the types of administration. **Figure 43** shows the percentage of the drug administration type presented in the clinical trials studies.





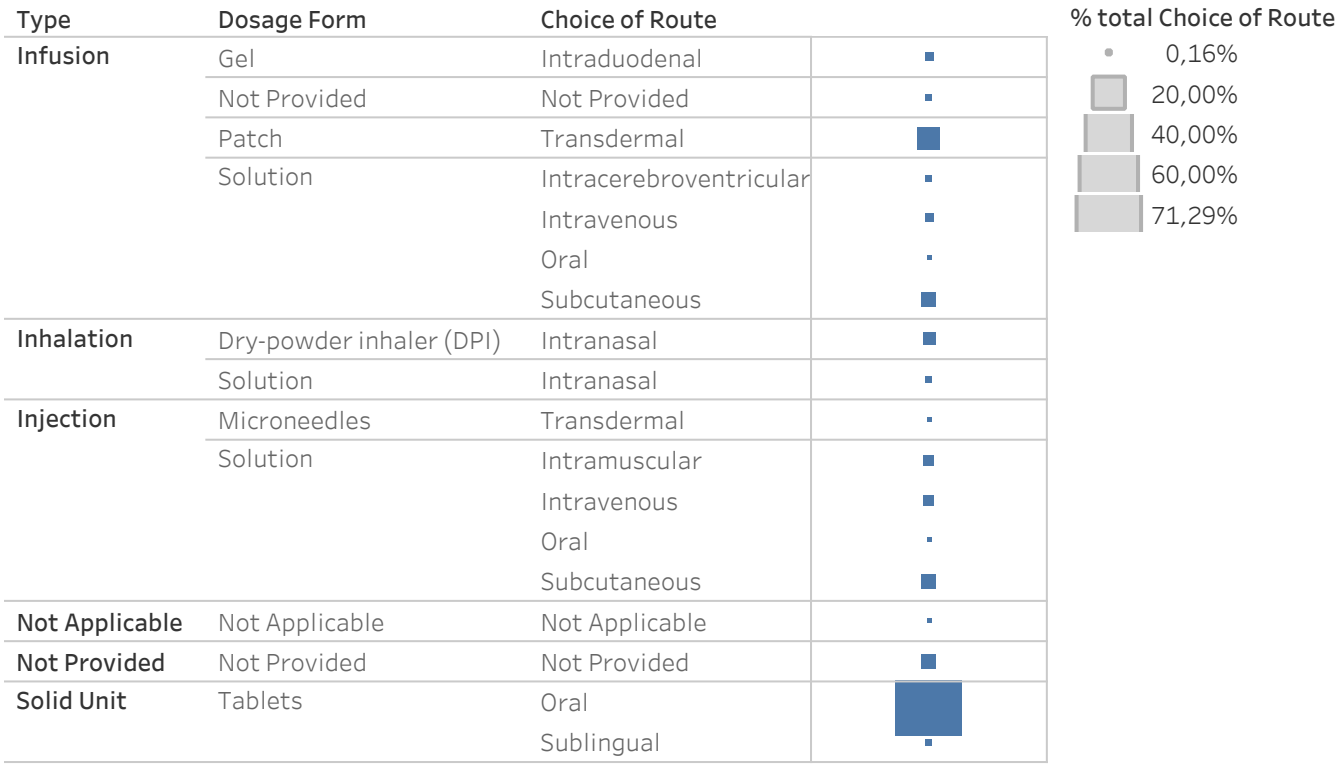
Drug Administration Type	% Total
Solid Unit	72,10%
Infusion	14,85%
Injection	6,69%
Inhalation	3,10%
Not Provided	3,10%
Not Applicable	0,16%

Figure 43. Drug Administration Type
The different types of administration are represented by different colors.
% of the different types of drug administration are presented in the table at the bottom right.

The different drug administration types considered are infusion, inhalation, injection and solid units. The figure shows a majority use of the solid units by 72,10% of the clinical trials.

The infusions are used in 14,85% of the clinical trials and the inhalation type are used in 3,10% of the clinical trial studies.

To summarize drug administration for PD in the last 20 years, the following figure is presented (**Figure 44**).



Type	Form	Route	% of Route choise
Solid Unit	Tablets	Oral	71,29%
Infusion	Patch	Transdermal	7,67%
Infusion	Solution	Subcutaneous	3,59%
Not Provided	Not Provided	Not Provided	3,10%
Injection	Solution	Subcutaneous	2,94%
Inhalation	Dry-powder inhaler (DPI)	Intranasal	2,45%
Injection	Solution	Intravenous	1,63%
Injection	Solution	Intramuscular	1,63%
Infusion	Solution	Intravenous	1,14%
Infusion	Gel	Intraduodenal	0,98%
Solid Unit	Tablets	Sublingual	0,82%
Infusion	Solution	Intracerebroventricular	0,65%
Inhalation	Solution	Intranasal	0,65%
Infusion	Not Provided	Not Provided	0,49%
Infusion	Solution	Oral	0,33%
Injection	Microneedles	Transdermal	0,33%
Injection	Solution	Oral	0,16%
Not Applicable	Not Applicable	Not Applicable	0,16%

Figure 44. Drug Administration Type Categorized By Drug Form And Drug Route
A summary of drug administration is presented.
The dimension of the square is related to the number of studies using the specified administration.
% of the different drug administrations are summarized in the table at the bottom right.

It is shown the all set of drug administration types, formulations and routes provided by all the clinical trials studies. The table present in the figure shows that the infusion type that is mostly used by patch form is by transdermal route (7.66%). The table also shows that the inhalation types are preferred in dry-power inhaler and by intranasal route (2,44%). Injections type is preferred in solution form and mainly administrated by subcutaneous route (2.93%). However, still the solid unit type is preferred in all 613 studies, and administered in tablets form by oral route (71.29%).

2.3. Data Collection, Management, And Analysis: From API To Drug And Target-Related Markers

Different molecules have been tested in PD. This era that started with Levodopa, which proved to be the most promising molecule. Notwithstanding, new candidates have appeared to complement the levodopa treatment or to deal with its side effects. Generally, and from 1998 to 2019, 191 APIs were studied. Apomorphine was presented in 3,752% of the studies. Istradefyline was presented in 2,610% of the studies. Levodopa was presented in 5,383% of the studies. Levodopa/Carbidopa was presented in 5,873% of the studies. Opicapone was presented in 5,873% of the studies. Perampanel was presented in 2,121% of the studies. Pramipexole was presented in 3,263% of the studies. Rasagiline was presented in 4,731% of the studies. Ropinirole was presented in 3,100% of the studies. Rotigotine was presented in 8,483% of the studies. Safinamide was presented in 2,610% of the studies. To systematize all the compound used in the past 20 years.

Figure 45 shows an overall panorama of the drugs developed.

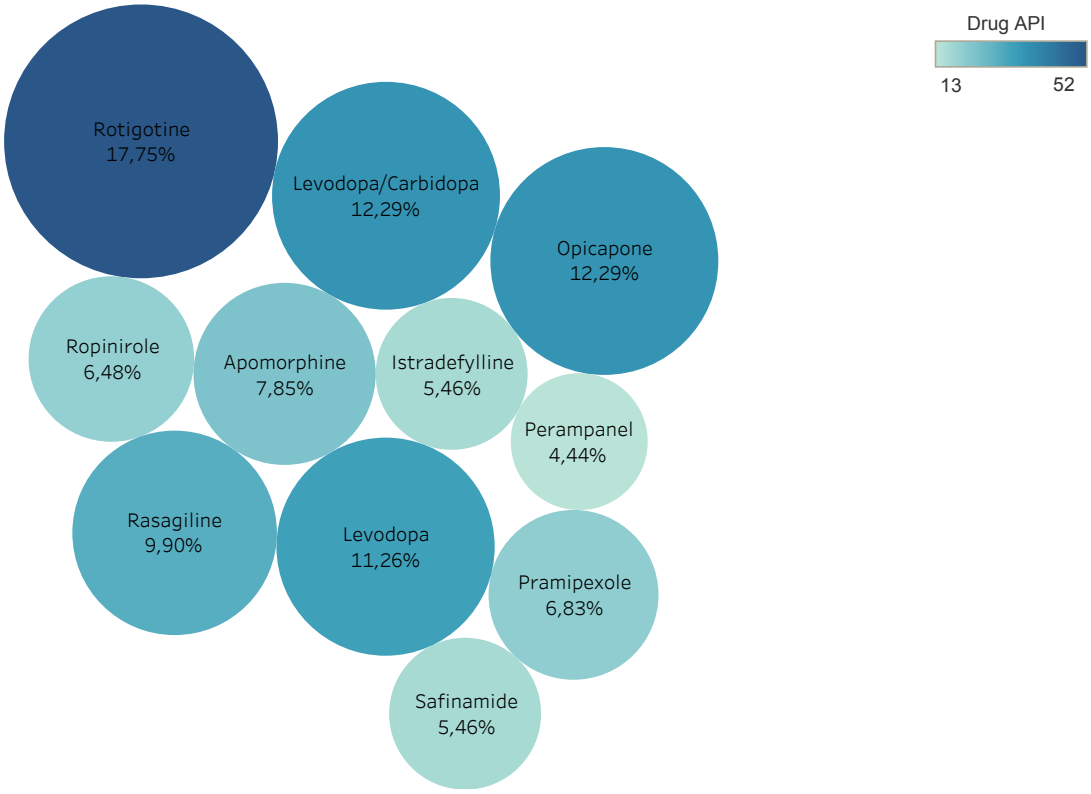


Figure 45. Principal Drug API
The color gradation from dark blue to light blue represent the most drug class used to the less drug API used, respectively.

To better categorize all the molecules in the PDCard Database, drugs were systemized accordingly to their Active Pharmaceutical Ingredient (API). The following plot shows only the most relevant APIs in the PD clinical trials population. Only drugs that were present in more than 13 studies were used.

The dark blue represents the most used drug in the clinical trials population. Rotigotine is the most studied drug in the trial's population with 17.75 % in the last 20 years.

Secondly, opicapone was used vastly and correspond to 12.29% of the studies; followed by Levodopa/Carbidopa combination, which was used in 12.29% of the studies.

Pure levodopa studies were used in 11,26% of the clinical trials. Rasagaline was tested in 9,90% of the clinical trials.

The different API used in the PD clinical drug development may although be classified as antiparkinsonians drugs or non-parkinsonians drugs. Antiparkinsonians drugs were specifically developed for PD, while non-parkinsonians drugs were drugs developed to other conditions and used in PD.

Figure 46 presents then the percentage of antiparkinsonians drugs vs. non-parkinsonians drugs classes in percentages.

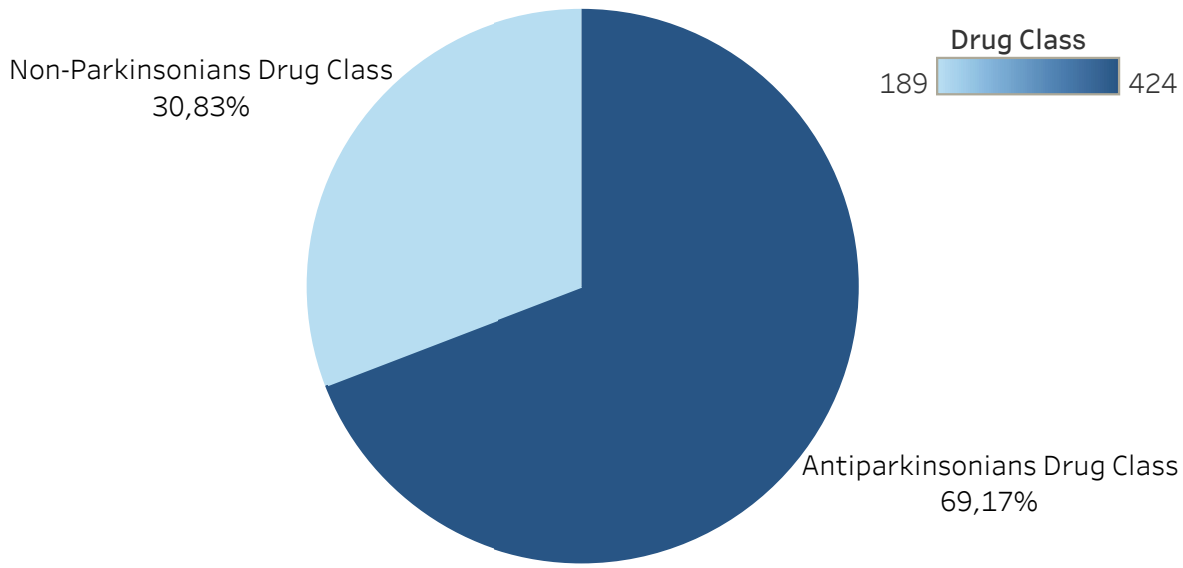
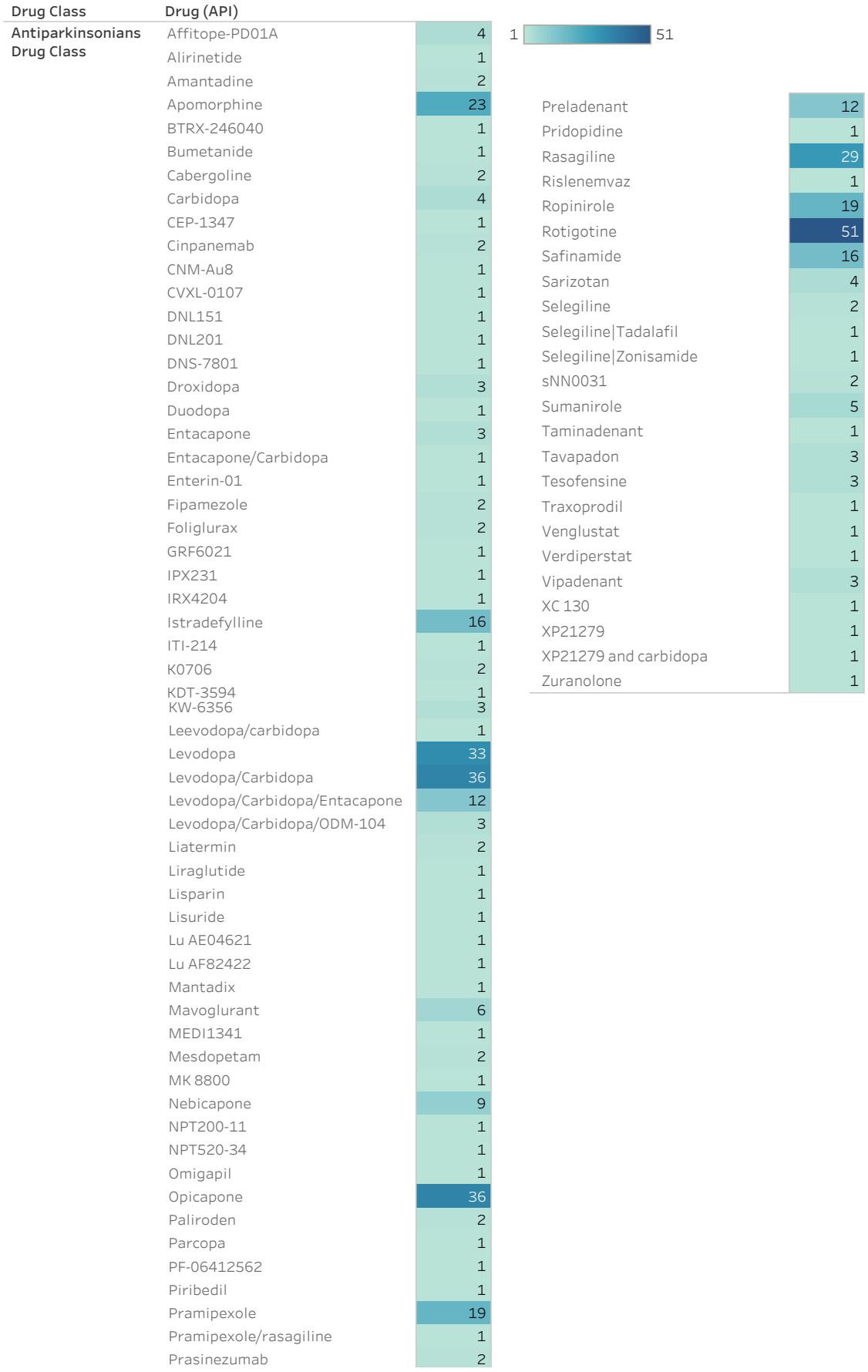


Figure 46. Antiparkinsonian And Non-Parkinsonian Drug Class
The pie chart presents the overall percentage of the two drug classes.
The gradient of blue is representative of the number of studies in each drug class.

PDCard Database included then 69,17% of all APIs which are considered antiparkinsonians drugs.

However, 30,83% are considered non-parkinsonians drugs and belong to another pharmacological class.

Additionally, a list of all the anti-parkinsonian drugs class systematized by drug API is presented (**Figure 47**).



Drug Class	Drug (API)	
Antiparkinsonians Drug Class	Affitope-PD01A	4
	Alirinetide	1
	Amantadine	2
	Apomorphine	23
	BTRX-246040	1
	Bumetanide	1
	Cabergoline	2
	Carbidopa	4
	CEP-1347	1
	Cinpanemab	2
	CNM-Au8	1
	CVXL-0107	1
	DNL151	1
	DNL201	1
	DNS-7801	1
	Droxidopa	3
	Duodopa	1
	Entacapone	3
	Entacapone/Carbidopa	1
	Enterin-01	1
	Fipamezole	2
	Foliglurax	2
	GRF6021	1
	IPX231	1
	IRX4204	1
	Istradefylline	16
	ITI-214	1
	K0706	2
	KDT-3594	1
	KW-6356	3
	Leevodopa/carbidopa	1
	Levodopa	33
	Levodopa/Carbidopa	36
	Levodopa/Carbidopa/Entacapone	12
	Levodopa/Carbidopa/ODM-104	3
	Liatermin	2
	Liraglutide	1
	Lisparin	1
	Lisuride	1
	Lu AE04621	1
	Lu AF82422	1
	Mantadix	1
	Mavoglurant	6
	MEDI1341	1
	Mesdopetam	2
	MK 8800	1
	Nebicapone	9
	NPT200-11	1
	NPT520-34	1
	Omigapil	1
	Opicapone	36
	Paliroden	2
	Parcopa	1
	PF-06412562	1
	Piribedil	1
	Pramipexole	19
	Pramipexole/rasagiline	1
	Prasinezumab	2
	Preladenant	12
	Pridopidine	1
	Rasagiline	29
	Rislenemvaz	1
	Ropinirole	19
	Rotigotine	51
	Safinamide	16
	Sarizotan	4
	Selegiline	2
	Selegiline|Tadalafil	1
	Selegiline|Zonisamide	1
	sNN0031	2
	Sumanirole	5
	Taminadenant	1
	Tavapadon	3
	Tesofensine	3
	Traxoprodil	1
	Venglustat	1
	Verdiperstat	1
	Vipadenant	3
	XC 130	1
	XP21279	1
	XP21279 and carbidopa	1
	Zuranolone	1

Figure 47. Antiparkinsonian Drug Class by Drug API
The gradient of blue is a correspondent to the number of API.

The most used APIs of antiparkinsonian drugs were apomorphine that was present in 23 studies, istradefyline in 16 studies, levodopa in 33 studies, levodopa/carbidopa in 36 studies, levodopa/carbidopa/entacapone in 12 studies, opicapone in 36 studies, pramipexole in 19 studies, preladenant in 12 studies, rasagiline in 29 studies, ropinirole in 19 studies, rotigotine in 51 studies, and safinamide in 16 studies.

If only the antiparkinsonians drugs are addressed, 26 drug classes are characterized. **Figure 48** presents thus the mechanisms of all the antiparkinsonians drugs presented in the PDCard Database.

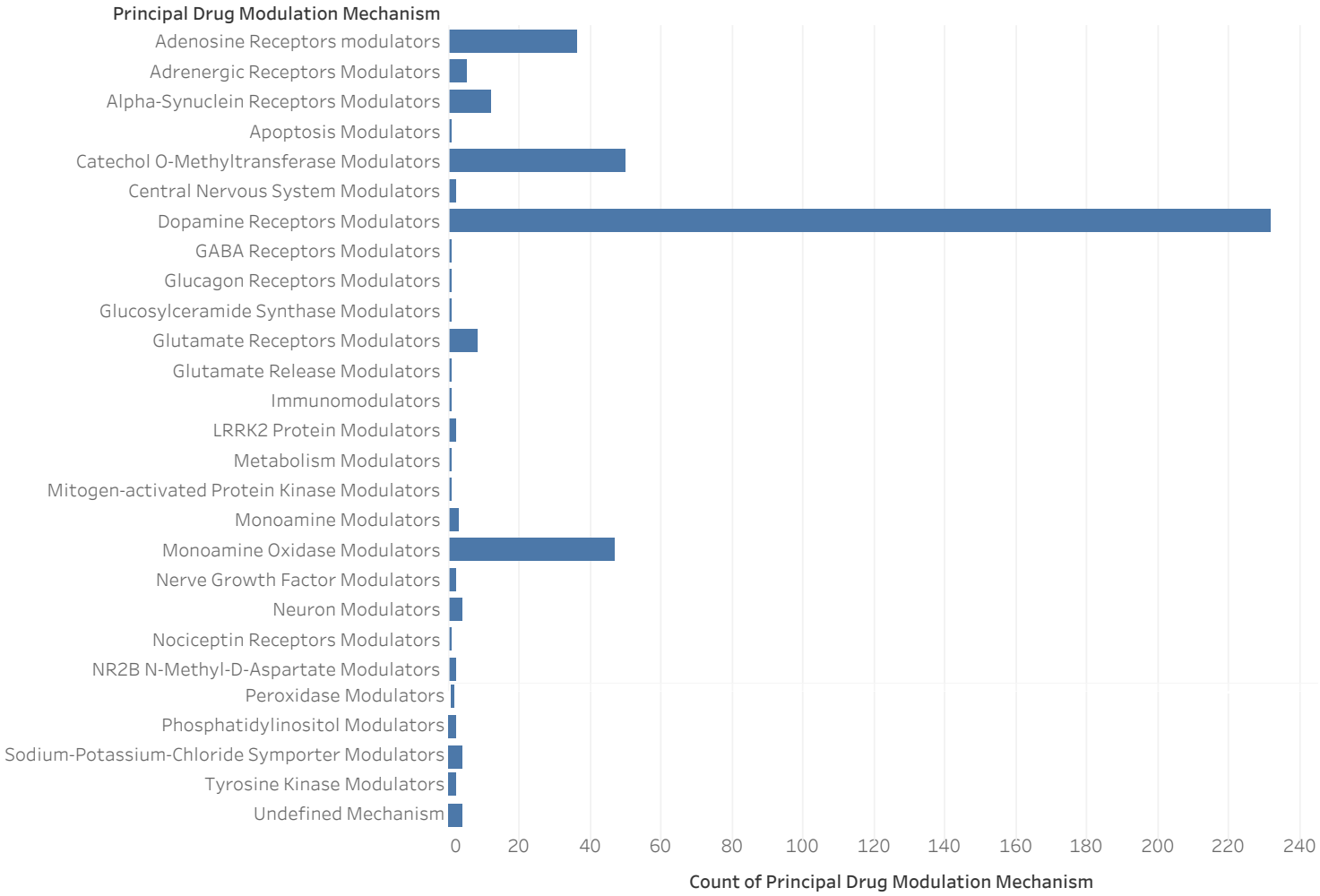


Figure 48. Drug Modulation Mechanism Of Antiparkinsonian Drugs
Chart plotting the number of studies for each drug class category.

Most of the API used in the last 20 years are dopamine receptor modulators, followed by catechol o-methyltransferase modulators, and tailed by monoamine oxidase modulators. Less present are adenosine receptor modulators, followed by alpha-synuclein receptor modulators, and tailed by glutamate receptor modulators.

Furthermore, it is important to address the full list of antiparkinsonians drugs used in the last 20 years. The following table **(Figure 49)** presents thus antiparkinsonians drugs in PDCard Database, specified by their API and sorted by principal drug modulation mechanism.

Principal Drug Modulation Mechanism	Drug (API)	
Adenosine Receptors modulators	Istradefylline	16
	ITI-214	1
	KW-6356	3
	Preladenant	12
	Taminadenant	1
	Vipadenant	3
Adrenergic Receptors Modulators	Droxidopa	3
	Fipamezole	2
Alpha-Synuclein Receptors Modulators	Affitope-PD01A	4
	Cinpanemab	2
	Enterin-01	1
	Lu AF82422	1
	MEDI1341	1
	NPT200-11	1
	Prasinezumab	2
Apoptosis Modulators	Omigapil	1
Catechol O-Methyltransferase Modulators	Entacapone	3
	Levodopa/Carbidopa/Entacapone	1
Catechol O-Methyltransferase Modulators	Nebicapone	9
	Opicapone	36
	Rasagiline	1
Central Nervous System Modulators	Mesdopetam	2
Dopamine Receptors Modulators	Amantadine	2
	Apomorphine	23
	Cabergoline	2
	Carbidopa	4
	Duodopa	1
	Entacapone/Carbidopa	1
	KDT-3594	1
	Leevodopa/carbidopa	1
	Levodopa	33
	Levodopa/Carbidopa	36
	Levodopa/Carbidopa/Entacapone	11
	Levodopa/Carbidopa/ODM-104	3
	Lisparin	1
	Lisuride	1
Dopamine Receptors Modulators	Lu AE04621	1
	Mantadix	1
	Parcopa	1
	PF-06412562	1
	Piribedil	1
	Pramipexole	19
	Pramipexole/rasagiline	1
	Pridopidine	1
	Ropinirole	19
	Rotigotine	51
	Sarizotan	4
	Selegiline|Zonisamide	1
	Sumanirole	5
	Tavapadon	3
	XC 130	1
	XP21279	1
	XP21279 and carbidopa	1
GABA Receptors Modulators	Zuranolone	1

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Principal Drug Modulation Mechanism	Drug (API)	
Glucagon Receptors Modulators	Liraglutide	1
Glucosylceramide Synthase Modulators	Venglustat	1
Glutamate Receptors Modulators	Foliglurax	2
	Mavoglurant	6
Glutamate Release Modulators	CVXL-0107	1
Immunomodulators	IRX4204	1
LRRK2 Protein Modulators	DNL151	1
	DNL201	1
Metabolism Modulators	CNM-Au8	1
Mitogen-activated Protein Kinase Modulators	CEP-1347	1
Monoamine Modulators	Tesofensine	3
Monoamine Oxidase Modulators	Rasagiline	28
	Safinamide	16
	Selegiline	2
	Selegiline|Tadalafil	1
Nerve Growth Factor Modulators	Paliroden	2
Neuron Modulators	Liatermin	2
	sNN0031	2
Nociceptin Receptors Modulators	BTRX-246040	1
NR2B N-Methyl-D-Aspartate Modulators	Rislenemvaz	1
	Traxoprodil	1
Peroxidase Modulators	Verdiperstat	1
Phosphatidylinositol Modulators	Alirinetide	1
	NPT520-34	1
Sodium-Potassium-Chloride Symporter Modulators	Bumetanide	1
Tyrosine Kinase Modulators	K0706	2
Undefined Mechanism	DNS-7801	1
	GRF6021	1
	IPX231	1
	MK 8800	1

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Figure 49. Drug Modulation Mechanism Of Antiparkinsonian Drugs By Drug API
The number of studies by API is represented and sorted by modulation mechanism.

Rotigotine (n. = 51 studies) is the API more represented, which belong to the dopamine receptor modulators.

Levodopa/carbidopa (n. = 36) is the API more represented, which also belongs to the dopamine receptor modulators.

Opicapone (n. = 36 studies) is the API that is more represented belonging to the Catechol O-Methyltransferase Modulators.

Rasagiline (n. = 28 studies) is the API that is more represented belonging to the Monoamine Oxidase Modulators.

A list of all the non-parkinsonian drugs class systematized by drug API is presented (**Figure 50**). Coenzyme Q10 was present in 6 studies, perampanel in 13 studies, rivastigmine in 5 studies, tozadenant in 5 studies, and trans-resveratrol was present in 7 studies.

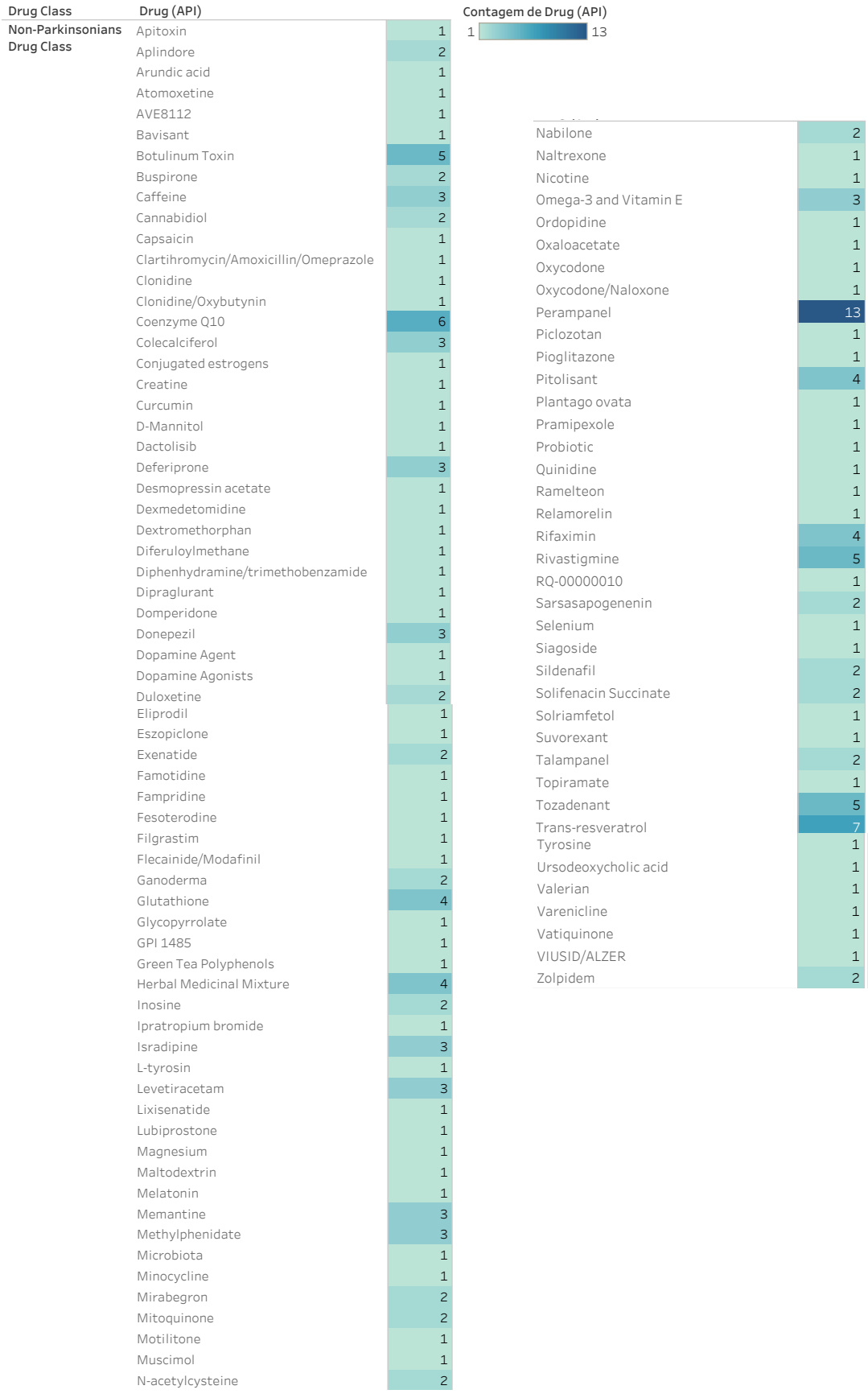


Figure 50. Non-Parkinsonian Drug Class By Drug API
The gradient of blue is a correspondent to the number of API.

Likewise, and if only the non-parkinsonians drugs are addressed, 47 drug classes are characterized. **Figure 51** presents thus the mechanisms of all the non-parkinsonians drugs presented in the PDCard Database.

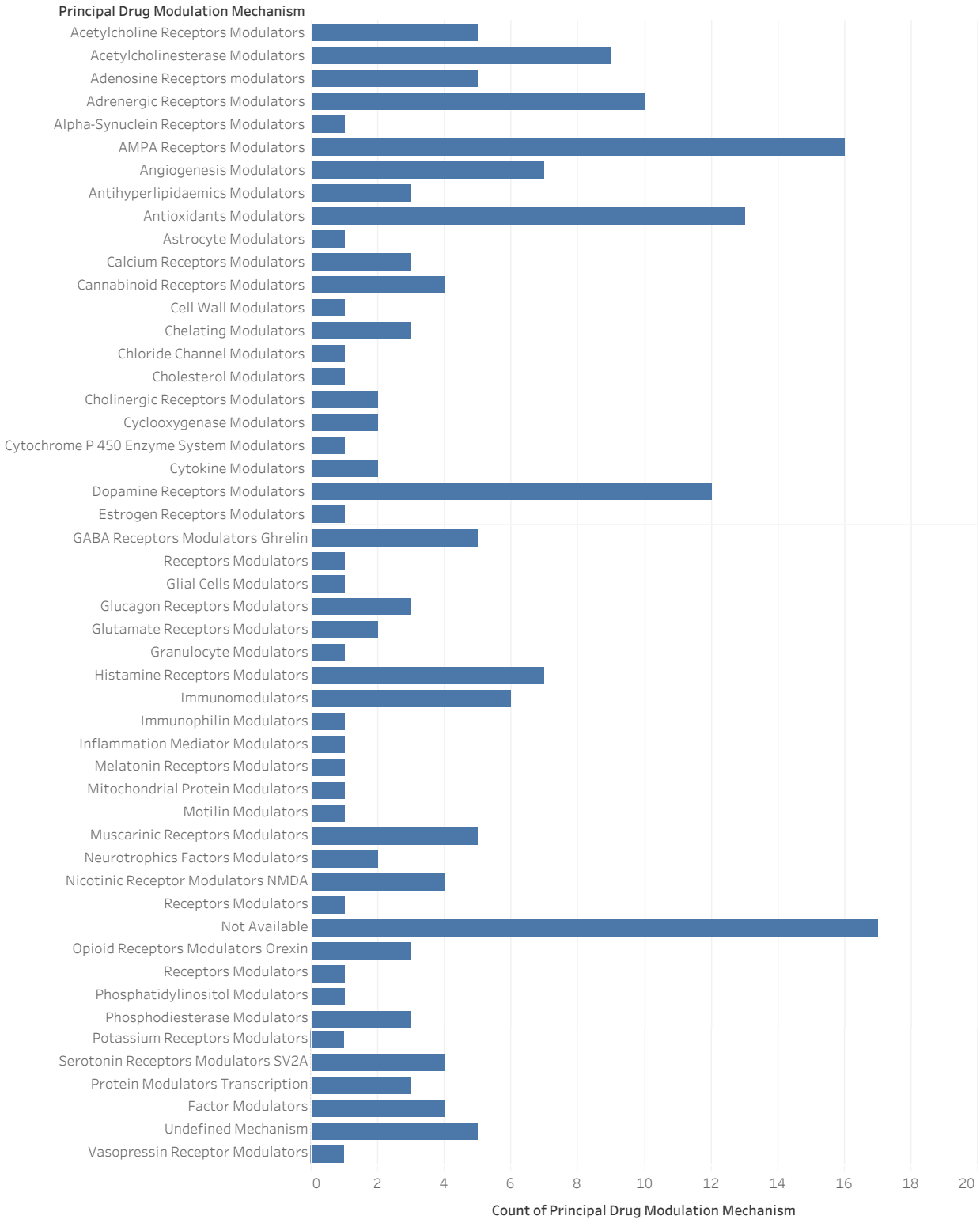


Figure 51. Drug Modulation Mechanism Of Non-parkinsonian Drugs Chart plotting the number of studies for each drug class category.

Most of the API used not specifically for PD in the last 20 years are AMPA receptor modulators, followed by antioxidant modulators, and tailed by dopamine modulators. Less present are adrenergic receptor modulators, followed by acetylcholinesterase modulators, and tailed by angiogenesis modulators.

Besides, it is also important to address the full list of non-parkinsonians drugs used in the last 20 years. The following table (**Figure 52**) presents thus non-parkinsonians drugs in PDCard Database, specified by their API and sorted by principal drug modulation mechanism.

Principal Drug Modulation Mechanism	Drug (API)	1 – 13
Acetylcholine Receptors Modulators	Botulinum Toxin	5
Acetylcholinesterase Modulators	Donepezil	3
	Duloxetine	1
	Rivastigmine	5
Adenosine Receptors modulators	Tozadenant	5
Adrenergic Receptors Modulators	Apitoxin	1
	Atomoxetine	1
	Clonidine	1
	Clonidine/Oxybutynin	1
	Dexmedetomidine	1
	Duloxetine	1
	Eliprodil	1
	Flecainide/Modafinil	1
	Mirabegron	2
Alpha-Synuclein Receptors Modulators	Varenicline	1
AMPA Receptors Modulators	Perampanel	13
	Talampanel	2
	Topiramate	1
Angiogenesis Modulators	Trans-resveratrol	7
Antihyperlipidaemics Modulators	Omega-3 and Vitamin E	3
Antioxidants Modulators	Coenzyme Q10	6
	D-Mannitol	1
	Melatonin	1
	Mitoquinone	2
	N-acetylcysteine	2
	Vatiquinone	1
Astrocyte Modulators	Arundic acid	1
Calcium Receptors Modulators	Isradipine	3
Cannabinoid Receptors Modulators	Cannabidiol	2
	Nabilone	2
Cell Wall Modulators	Clartihromycin/Amoxicillin/Omeprazole	1
Chelating Modulators	Deferiprone	3
Chloride Channel Modulators	Lubiprostone	1
Cholesterol Modulators	Ursodeoxycholic acid	1
Cholinergic Receptors Modulators	Tropicamide	2
Cyclooxygenase Modulators	Caffeine	2
Cytochrome P 450 Enzyme System Modulators	Quinidine	1
Cytokine Modulators	Inosine	2
Dopamine Receptors Modulators	Aplindore	2
	Domperidone	1
	Dopamine Agent	1
	Dopamine Agonists	1
	Methylphenidate	3
	Ordopidine	1
	Pramipexole	1
Glutamate Receptors Modulators	Dipraglurant	1
	Oxaloacetate	1
Granulocyte Modulators	Filgrastim	1
Histamine Receptors Modulators	Bavisant	1
	Diphenhydramine/trimethobenzamide	1
	Famotidine	1
	Pitolisant	4
Immunomodulators	Ganoderma	1
	Glutathione	4
	Probiotic	1
Immunophilin Modulators	GPI 1485	1
Inflammation Mediator Modulators	Pioglitazone	1
Melatonin Receptors Modulators	Ramelteon	1
Mitochondrial Protein Modulators	Creatine	1
Motilin Modulators	Motilitone	1
Muscarinic Receptors Modulators	Fesoterodine	1
	Glycopyrrolate	1
	Ipratropium bromide	1
	Solifenacin Succinate	2
Neurotrophics Factors Modulators	Sarsasapogenenin	2
Nicotinic Receptor Modulators	Memantine	3
	Nicotine	1
NMDA Receptors Modulators	Dextromethorphan	1
Not Available	Caffeine	1
	Curcumin	1
	Diferuloylmethane	1
	Ganoderma	1
	Green Tea Polyphenols	1
	Herbal Medicinal Mixture	4
	L-tyrosin	1
	Magnesium	1
	Maltodextrin	1
	Microbiota	1
	Plantago ovata	1
	Tyrosine	1
	Valerian	1
	VIUSID/ALZER	1
Opioid Receptors Modulators	Naltrexone	1
	Oxycodone	1
	Oxycodone/Naloxone	1
Orexin Receptors Modulators	Suvorexant	1
Phosphatidylinositol Modulators	Dactolisib	1
Phosphodiesterase Modulators	AVE8112	1
	Sildenafil	2
Potassium Receptors Modulators	Fampridine	1
Serotonin Receptors Modulators	Buspirone	2
	Piclozotan	1
	RQ-00000010	1
SV2A Protein Modulators	Levetiracetam	3
Transcription Factor Modulators	Rifaximin	4
Undefined Mechanism	Colecalciferol	3
	Selenium	1
	Siagoside	1
Vasopressin Receptor Modulators	Desmopressin acetate	1

Figure 52. Drug Mechanism Of Non-Parkinsonian Drugs By Drug API
The number of studies by API is represented and sorted by modulation mechanism.

Perampanel (n. = 13 studies) is the API more represented, which belong to the AMPA receptors modulators. Trans-resveratrol (n. = 7) is the API more represented, which belongs to angiogenesis modulators. Coenzyme Q10 (n. = 3 studies) is the API that is more represented belonging to the antioxidant modulators. Glutathione (n. = 4 studies) is the API that is more represented belonging to the Immunomodulators.

However, some APIs were considered new to market and were not used before neither in PD, neither on other medical conditions. Indeed, as shown in **Figure 53**, from all the API, 46,17% are new molecular entities, while 51,71% are drugs that already existed in the market and were tested in PD disease.

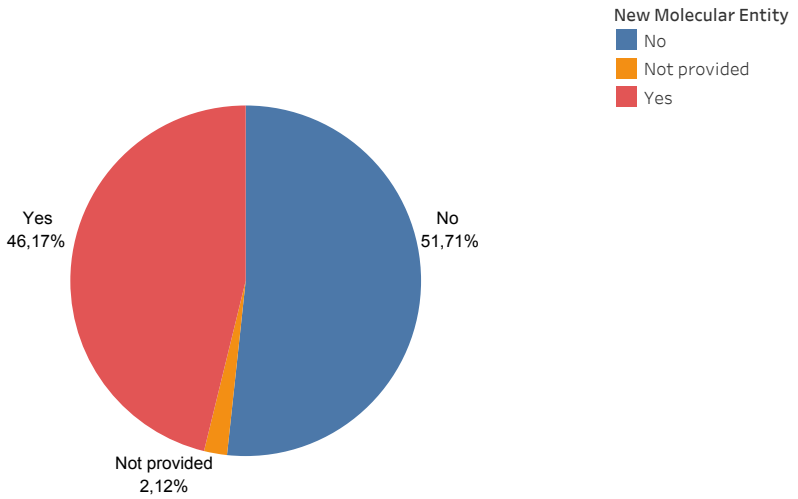


Figure 53. New Molecular Entity
Three colors are provided for each element. % of the total number of studies is presented for the new molecular entities.

Furthermore, some of these APIs have been considered the status of an orphan drug for different conditions, including PD (**Figure 54**).

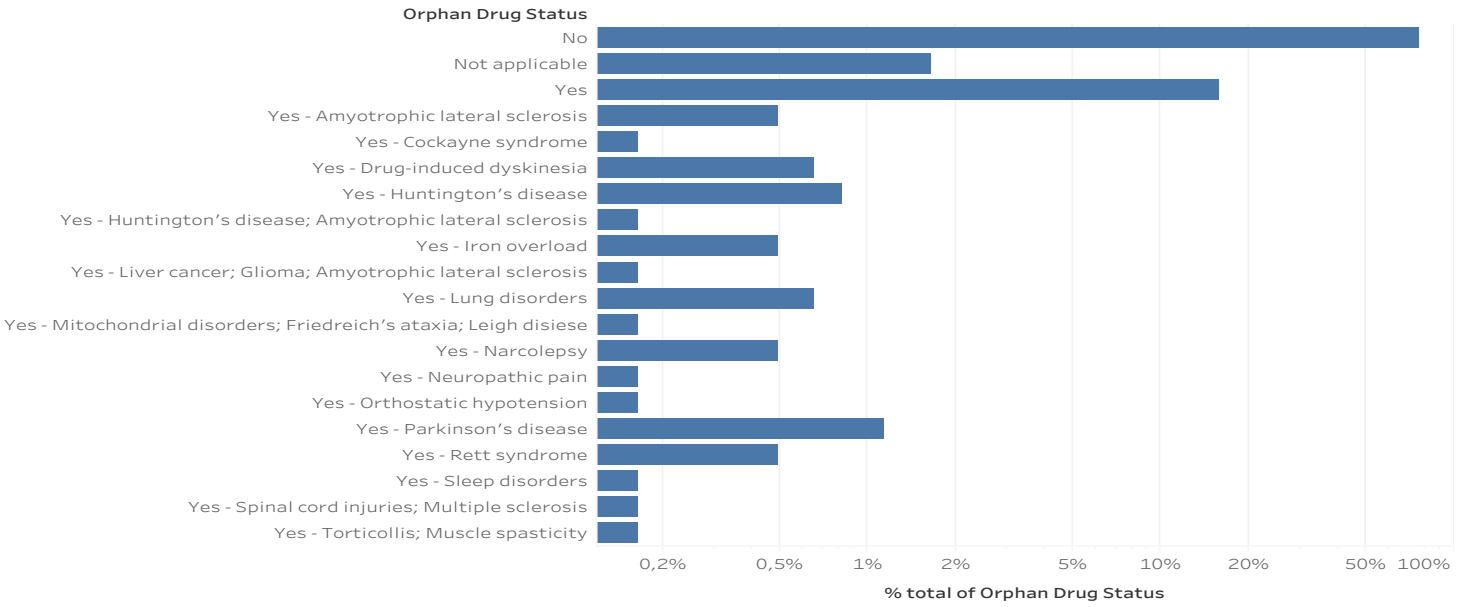


Figure 54. Orphan Drug Status
Relative percentage of API considered orphan drugs are potted horizontally.
Seventeen different medical conditions are presented.

Figure 54 shows that 76% of the API used in the 613 studies were not considered an orphan drug.

However, 22% of drugs were considered the status of an orphan drug. For Parkinson disease, 1,14% of all API had the orphan drug status.

One of the main interests in PD drug development is to understand what type of marker is used to monitor the drug effect.

Firstly, if considered the API and sorted by study phase, in Phase 1, 7 molecules studied drug-related markers.

In Phase 1|2, 4 molecules studied drug-related markers. In Phase 2, 18 molecules studied drug-related markers.

In Phase 2|3, 4 molecules studied drug-related markers.

In Phase 3, 2 molecules studied drug-related markers. In Phase 3, 2 molecules studied drug-related markers.

In Phase 4, 12 molecules studied drug-related markers.

As debated in the introduction, there are four main types of biomarkers: clinical, imaging, biochemical, and genetic. The studies that monitor the outcomes by using drug markers produce drugs and target related markers.

Figure 55 shows the presence or absence of the drug and target-related markers in the 613 clinical trials. The figure shows that most of the trials have not been designed for drugs or target-related markers. Indeed, only 7,99% of the studies show the presence of the drug and related markers.

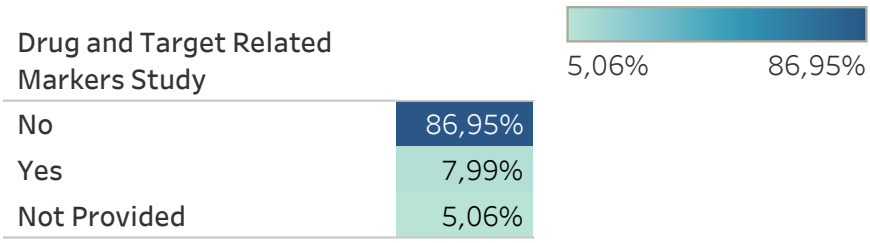


Figure 55. Drug And Target Related Markers Studies
The gradient of blue represents the relative percentage of the marker.

Parallelly, **Figure 56** shows indeed that most of the trials (67,05%) have focused rather on non-drug target-related markers, for instance on clinical scales like the MDS-UPDRS.

However, 27,90% of the studies still present no non-drug target-related markers. Those are usually phase 1 studies that have as primary outcome the evaluation of safety.

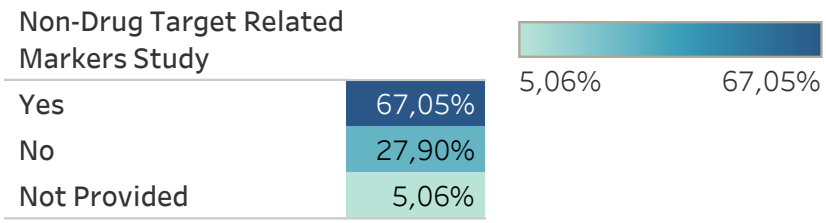


Figure 56. Non-Drug Target Related Markers Study
The gradient of blue represents the relative percentage of the marker.

In drug development there has been an increasing interest to monitor outcomes with biomarkers. To better address biomarker monitoring in the last 20 years of PD drug development **Figure 57** shows the biomarker type or class, stacked by the study phase.

From all the drug-related biomarkers, imaging biomarkers are the most representative (n. = 24) and phase 2 and phase 4 were the ones that study more biomarkers.

From all the drug-related biomarkers, biochemical is the 2nd most representative (n. = 13) and phase 2 is the ones that study more biomarkers.

From all the drug-related biomarkers, clinical biomarkers are the 3rd most representative (n. = 9) and phase 4 is the ones that produce more biomarkers.

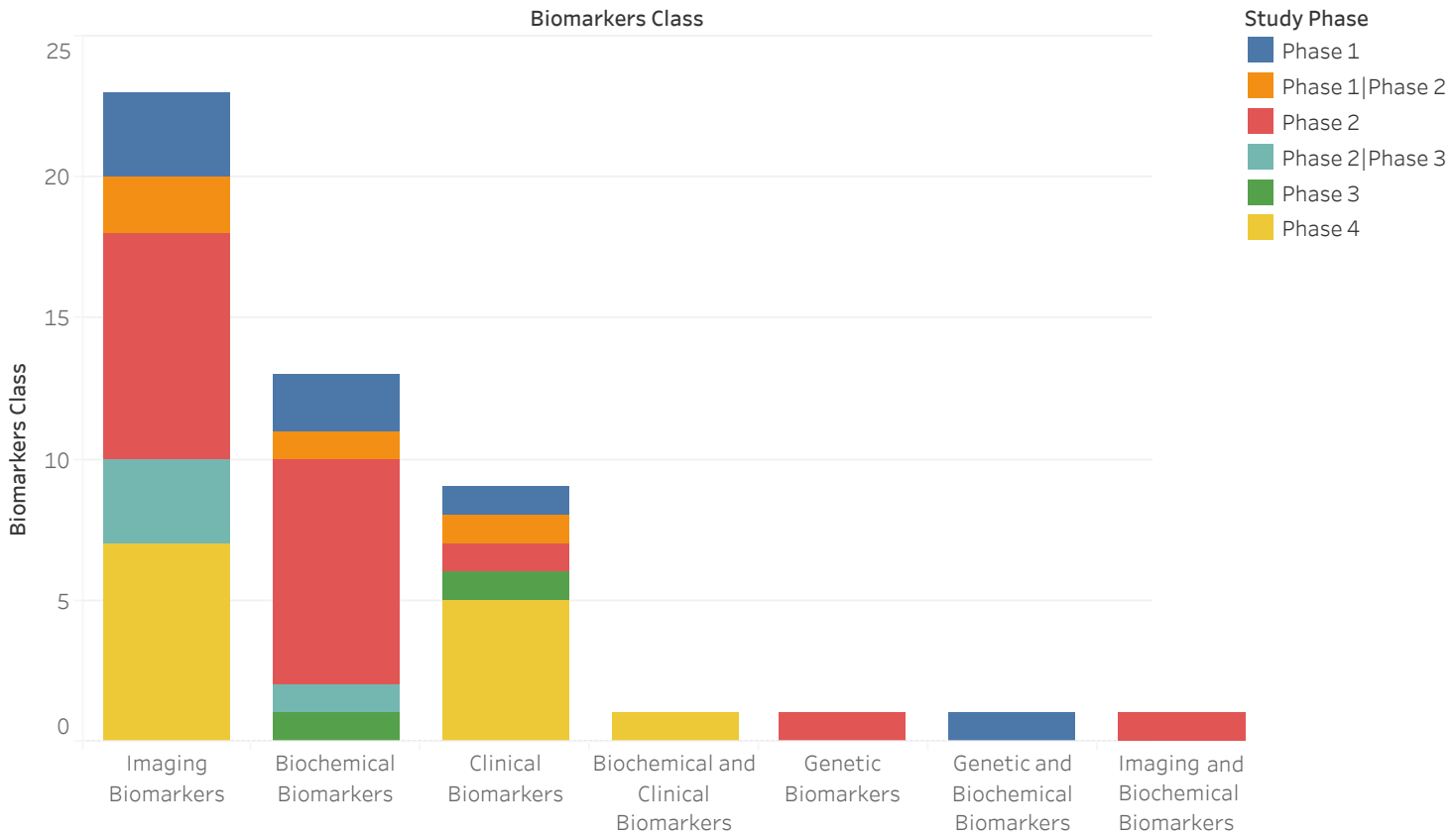


Figure 57. Biomarkers Class stacked By Study Phase (1-4)
The y-axis shows the number biomarkers.
The color shows the different PD stages.

In order to better detail the biomarkers that was used, **Figure 58** show an overview of the analytes used to study the drug-related biomarker, sorted by class or type of biomarker.

Imaging biomarkers are the ones that are more studied and magnetic resonance imaging is the technique most used (8 studies).

Clinical Biomarkers are the second most studies and polysomnography the technique more utilized (4 studies).

Biochemical biomarkers are the 3rd most studied biomarkers and blood biomarkers (3 studies) and ELISA (3 studies) the analysis mostly used.

Genetic biomarkers are studied through PCR. Some studies utilized the combination of both imaging and biochemical biomarkers, biochemical and clinical biomarkers, or genetic and biochemical biomarkers.

Biomarkers Class	Biomarkers Description
Imaging Biomarkers	[123I]IBZM receptor SPECT
	CIT/SPECT
	DATScan
	DaTscan and Optoelectronic System
	Dopamine-transporter SPECT (DAT-SPECT)
	Electroencephalography
	Emission Computed Tomography (SPECT)
	Magnetic resonance imaging
	Magnetic Resonance Spectroscopy
	Positron emission tomography
	Positron Emission Tomography (PET) Scan
Clinical Biomarkers	Forceplate
	Parkinson's Kinetigraph (PKG)
	Polysomnography
	Spirometry
	Timed-Up-and-Go (TUG) duration
Biochemical Biomarkers	Blood biomarkers
	Electrochemical Detection (ECD)
	Enzyme-linked Immunosorbent Assay (ELISA)
	Enzyme-linked Immunosorbent Assay (ELISA) and Enzymatic kit
	Homeostasis Model Assessment (HoMA-IR) index
	Plasma F2-isoprostanes
	S-COMT activity
	Smart Pill¬Æ (SP) Wireless pH/pressure recording capsule
	Spectrophotometry and Enzyme-linked Immunosorbent Assay (ELISA)
Genetic Biomarkers	Polymerase Chain Reaction (PCR)
Imaging and Biochemical Biomarkers	Magnetic Resonance spectroscopy and Electroretinogram
Biochemical and Clinical Biomarkers	Cholinersterase Inhibitor Prognosticator and EEG power analysis
Genetic and Biochemical Biomarkers	Shannon Diversity Index and Smart Pill Æ (SP) Wireless pH/pressure recording capsule

Figure 58. Biomarkers Technique Description Sorted By Biomarkers Class
The size of the squares is a correspondent to the number of biomarkers.

Complementarily, **Figure 59** lists the description of the drug-related biomarkers and sorted by the biomarker class.

On the first column, the biomarker class is presented. On the second column, a brief description of the technique is explained. On the third column, a full description of the observed effect is detailed.

For instance, in the section imaging biomarkers, one study used CIT/SPECT to study directly the striatal uptake levels.

In the section biochemical biomarkers, one study used S-COMT activity to measure the plasma concentration of levodopa, opicapone and its metabolites.

In the section clinical biomarkers, one study used Parkinson's Kinetograph for dyskinesia measurement.

Biomarkers Class	Biomarkers Description	Biomarkers Description
Biochemical and Clinical Biomarkers	Cholinersterase Inhibitor Prognosticator and EEG power analysis	Changes in visual hallucinations frequency
Biochemical Biomarkers	Blood biomarkers	Blood biomarkers of neuroinflammation and exosomal alpha-synuclein concentration
		Drug blood level profiles
		Plasma concentration of LD and CD following SC ND-0612 administration
	Electrochemical Detection (ECD)	Red blood cell Glutathione levels
	Enzyme-linked Immunosorbent Assay (ELISA)	Hs-CRP
		Ratio of total-to-proteinase K-resistant α-Syn levels in red blood cells
		Serum levels of LDL
	Enzyme-linked Immunosorbent Assay (ELISA) and Enzymatic kit	High-sensitivity C-reactive protein concentration, insulin resistance and fasting plasma glucose levels
	Homeostasis Model Assessment (HoMA-IR) index	Peripheral insulin resistance
	Plasma F2-isoprostanes	Biomarkers concentration of oxidative damage
	S-COMT activity	Plasma concentration of levodopa, opicapone and its metabolites
	Smart Pill¬Æ (SP) Wireless pH/pressure recording capsule	Changes in gastric emptying time, small bowel transit time, colon transit time, small/large bowel transit time, whole gut transit time
	Spectrophotometry and Enzyme-linked Immunosorbent Assay (ELISA)	High sensitivity C-reactive protein (hs-CRP) concentration, total antioxidant capacity and insulin resistance
Clinical Biomarkers	Forceplate	Dyskinesia measurement
	Parkinson's Kinetigraph (PKG)	Dyskinesia measurement
	Polysomnography	Effect of safinamide on objective PSG sleep characterization
		Home sleep monitoring of oxygenation from polysomnography. Objective sleep quality from polysomnography
		Monitoring of oxygenation from polysomnography. Objective sleep quality from polysomnography
		Oxygenation from polysomnography. Objective sleep quality from polysomnography
	Spirometry	FEV1 measurement
	Timed-Up-and-Go (TUG) duration	Timed-Up-and-Go (TUG) duration

Biomarkers Class	Biomarkers Description	Biomarkers Description 1
Genetic and Biochemical Biomarkers	Shannon Diversity Index and Smart Pill Æ (SP) Wireless pH/pressure recording capsule	Genetic microbiome diversity in fecal Samples acessed by Shannon Diversity Index
Genetic Biomarkers	Polymerase Chain Reaction (PCR)	Tumor necrosis factor alpha concentration
Imaging and Biochemical Biomarkers	Magnetic Resonance spectroscopy and Electroretinogram	Brain metabolites, blood biomarker levels and visual function measurement
Imaging Biomarkers	[123I]IBZM receptor SPECT	Change in Striatal, Caudate and Putamen [123I]-IBZM Binding following a single dose of Carbidopa/Levodopa.
	CIT/SPECT	Striatal uptake levels
	DATScan	Striatal binding ratio
	DaTscan and Optoelectronic System	Strength of axial flexor and extensor and stride length by gait analysis
	Dopamine-transporter SPECT (DAT-SPECT)	The percent change of SBR of DAT-SPECT
	Electroencephalography	To evaluate the mean latency of the P300 component of the event-related potentials
	Emission Computed Tomography (SPECT)	Percentage change from baseline in the striatum uptake
	Magnetic resonance imaging	Change in oxygen extraction on MRI.
		Change of gastric motility measurement
		Confirmation of distributing muscimol concentration
		Decrease the iron overload in the substantia nigra. Modification of T2* in MRI of the caudal nucleus head, putamen and pallidum.
		Effects of SYN115 levels in brain
		Free-water accumulation (substantia nigra), blood oxygen level-dependent signal (Posterior putamen), blood oxygen level-dependent signal (M1)
		Progression of neuromelanin-related MRI signal
		Resting-state brain network
	Magnetic Resonance Spectroscopy	Cerebral glutathione levels
		Cerebral redox markers concentration
		Glutathione brain levels
	Positron emission tomography	18F-flurodeoxyglucose concentration
	Positron Emission Tomography (PET) Scan	Change in average (left and right) putamen 18F-Dopa influx constant (Ki) from baseline to two year 18F-Dopa PET
		Change in caudate and putamen dopamine turnover
		Fluoro-Dopa-PET levels in the putamen
		Striatal 11C-raclopride BP levels

Figure 59. Target Biomarker Description categorized by Biomarker Class

3. Exploratory Analysis Of The Success And Failure Cases In PD Drug Development

The 613 studies were sorted, and when Phase 1 was selected, 47 different APIs were present. When Phase 2 was selected, 106 different APIs were present. When Phase 1|2 was selected, 20 different APIs were present. When Phase 3 was selected, 42 different APIs were present. When Phase 2|3 was selected, 18 different APIs are present. When Phase 4 was selected, 35 different APIs are present.

Then, manually, each of the 187 molecules, or APIs, was individually identified as a success or failure case. Afterwards, four timepoints were defined to simplify the analysis of the success and failure rates. T_1 was defined for the transition from Phase 1 to Phase 2. T_2 was defined for the transition from Phase 2 and 1|2 to Phase 3. T_3 was defined for the transition from Phase 3 and 2|3 to Phase 4. T_4 was defined for the transition from Phase 4 to Postmarketing Surveillance (PMS).

Success rates will be calculated accordingly to this function:

$$f(\text{success rate}) = f(\alpha) = x / z,$$

x is equal to the number of compounds that passed successfully in T_α
z is equal to total number of compounds in T_α
α is the timepoint of the analysis

Failure rates will be calculated accordingly to this function:

$$\delta\ (\text{failure rate}) = \delta(\alpha) = x / z,$$

x is equal to the number of compounds that failed to advance in T_α
z is equal to total number of compounds in T_α
α is the timepoint of the analysis

3.1. Analysis Of Success And Failure Rates In T_1 Phase 1 To Phase 2

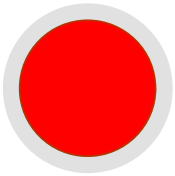
From the analysis of the PDCard Database, 19 compounds passed successfully from phase 1 to phase 2. 28 compound failed to pass from phase 1 to phase 2. A total number of 47 compounds are present in timepoint T_1.

$$f(\text{success rate}) = f(x) = x / z \Leftrightarrow f(19) = x / 47 \Leftrightarrow \text{success rate} = 40\%$$

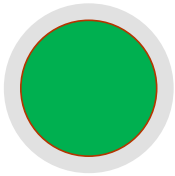
$$\delta\ (\text{failure rate}) = \delta(x) = x / z \Leftrightarrow \delta\ (28) = x / 47 \Leftrightarrow \text{failure rate} = 60\%$$

In conclusion, and from phase 1 to phase 2, the success rate is 40% and the failure rate is 60%.

The molecules that succeeded and failed to advance from phase 1 to phase 2 are presented in **Figure 60.**



Failure



Success

Affitope-PD01A
AVE8112
Buspirone
Cinpanemab
DNL151
DNL201
IPX231
IRX4204
Levodopa/Carbidopa/ODM-104
Liatermin
Lu AE04621
Lu AF82422
MEDI1341
Microbiota
MK 8800
Muscimol
NPT200-11
NPT520-34
Ordopidine
PF-06412562
Plantago ovata
Prasinezumab
Rislenemvaz
RQ-00000010
sNN0031
Taminadenant
Trans-resveratrol
XC 130

Phase 1 to Phase 2

Success Rate = 40%

Apomorphine
Carbidopa
Exenatide
Glutathione
Herbal Medicinal Mixture
K0706
KW-6356
Levodopa
Levodopa/Carbidopa
Levodopa/Carbidopa/Entacapone
Nebicapone
Opicapone
Pramipexole
Preladenant
Rasagiline
Rivastigmine
Ropinirole
Rotigotine
Sarsasapogenenin

Figure 60. Success Vs. Failure Analysis In Phase 1 To Phase 2
Two columns of list are provided. On the left the compounds that failed to progress to phase 2. On the right, the compounds that progressed.

Therefore, from phase 1 to phase 2, the following molecules succeeded to advance: Apomorphine, Carbidopa, Exenatide, Glutathione, Herbal Medicinal Mixture, K0706, KW-6356, Levodopa, Levodopa/Carbidopa, Levodopa/Carbidopa/Entacapone, Nebicapone, Opicapone, Pramipexole, Preladenant, Rasagiline, Rivastigmine, Ropinirole, Rotigotine and Sarsasapogenenin.

Consequently, from phase 1 to phase 2, the following molecules failed to advance: Affitope-PD01A, AVE8112, Buspirone, Cinpanemab, DNL151, DNL201, IPX231 , IRX4204, Levodopa/Carbidopa/ODM-104, Liatermin, Lu AE04621, Lu AF82422, MEDI1341, Microbiota, MK 8800, Muscimol, NPT200-11, NPT520-34, Ordopidine, PF-06412562, Plantago ovata, Prasinezumab, Rislenemvaz, RQ-00000010 , sNN0031, Taminadenant, Trans-resveratrol and XC 130.

3.2. Analysis Of Success And Failure Rates In T_2 Phase 2 And 1|2 To Phase 3

From the analysis of the PDCard Database, 24 compounds passed successfully from phase 2 and 1|2 to phase 3. 96 compound failed to pass from phase 2 and 1|2 to phase 3. A total number of 120 compounds are present in timepoint T_2.

$$f(\text{success rate}) = f(x) = x / z \Leftrightarrow f(24) = x / 120 \Leftrightarrow \text{success rate} = 20\%$$

$$\delta(\text{failure rate}) = \delta(x) = x / z \Leftrightarrow \delta(96) = x / 120 \Leftrightarrow \text{failure rate} = 80\%$$

In conclusion, and from phase 2 and 1|2 to phase 3, the success rate is 20% and the failure rate is 60%.

The molecules that succeeded and failed to advance from phase 2 and 1|2 to phase 3 are presented in **Figure 61.**

Figure 61. Success Vs. Failure Analysis In Phase 2 And 1|2 To Phase 3
Two columns of list are provided. On the left the compounds that failed to progress to phase 3. On the right, the compounds that progressed.

Therefore, from phase 2 and 1|2 to phase 3, the following molecules succeeded to advance: Apomorphine**,** Botulinum Toxin **,** Coenzyme Q10**,** Ganoderma**,** Isradipine**,** Istradefylline**,** Levodopa**,** Levodopa/Carbidopa**,** Levodopa/Carbidopa/Entacapone, Nabilone, Omega-3 and Vitamin E, Opicapone, Perampanel, Pitolisant, Pramipexole, Preladenant, Rasagiline, Rifaximin, Rivastigmine, Ropinirole, Rotigotine, Sarizotan, Sumanirole and Tozadenant.

Consequently, from phase 2 and 1|2 to phase 3, the following molecules failed to advance: Alirinetide, Apitoxin, Aplindore, Arundic acid, Bavisant, BTRX-246040**,** Bumetanide, Caffeine, Cannabidiol, Capsaicin, Carbidopa, Clonidine, Clonidine/Oxybutynin, CNM-Au8, Colecalciferol, Conjugated estrogens, CVXL-0107**,** D-Mannitol, Dactolisib, Deferiprone, Dextromethorphan, Dipraglurant, DNS-7801, Domperidone, Droxidopa, Duloxetine , Duodopa, Eliprodil, Entacapone Entacapone/Carbidopa, Enterin-01, Exenatide, Famotidine, Fampridine, Filgrastim, Fipamezole, Flecainide/Modafinil, Foliglurax, Glutathione, Glycopyrrolate, GPI 1485, Green Tea Polyphenols, GRF6021, Herbal Medicinal Mixture, Inosine, Ipratropium bromide, ITI-214, K0706, KDT-3594, KW-6356, L-tyrosin, Levetiracetam, Liatermin

Liraglutide, Lixisenatide, Maltodextrin, Mavoglurant, Melatonin, Mesdopetam, Methylphenidate, Minocycline, Mitoquinone, N-acetylcysteine, Nebicapone, Nicotine, Omigapil, Paliroden, Piclozotan, Pioglitazone, Pridopidine, Probiotic, Quinidine Relamorelin, Sarsasapogenenin, Selegiline|Zonisamide, Siagoside, Sildenafil, sNN0031, Solriamfetol, Talampanel, Tavapadon, Tesofensine, Topiramate, Traxoprodil, Tropicamide, Tyrosine, Ursodeoxycholic acid, Valerian, Vatiquinone, Venglustat, Verdiperstat, Vipadenant, XP21279, XP21279 and carbidopa, Zolpidem and Zuranolone.

3.3. Analysis Of Success And Failure Rate In T_3 Phase 3 And 2|3 To Phase 4

From the analysis of the PDCard Database, 15 compounds passed successfully from phase 3 and 2|3 to phase 4. 36 compound failed to pass from phase 3 and 2|3 to phase 4. A total number of 51 compounds are present in timepoint T_3.

$$f(\text{success rate}) = f(x) = x / z \Leftrightarrow f(15) = x / 51 \Leftrightarrow \text{success rate} = 29\%$$

$$\delta(\text{failure rate}) = \delta(x) = x / z \Leftrightarrow \delta(36) = x / 51 \Leftrightarrow \text{failure rate} = 71\%$$

In conclusion, and from phase 3 and 2|3 to phase 4, the success rate is 29% and the failure rate is 71%.

The molecules that succeeded and failed to advance from phase 3 and 2|3 to phase 4 are presented in **Figure 62.**

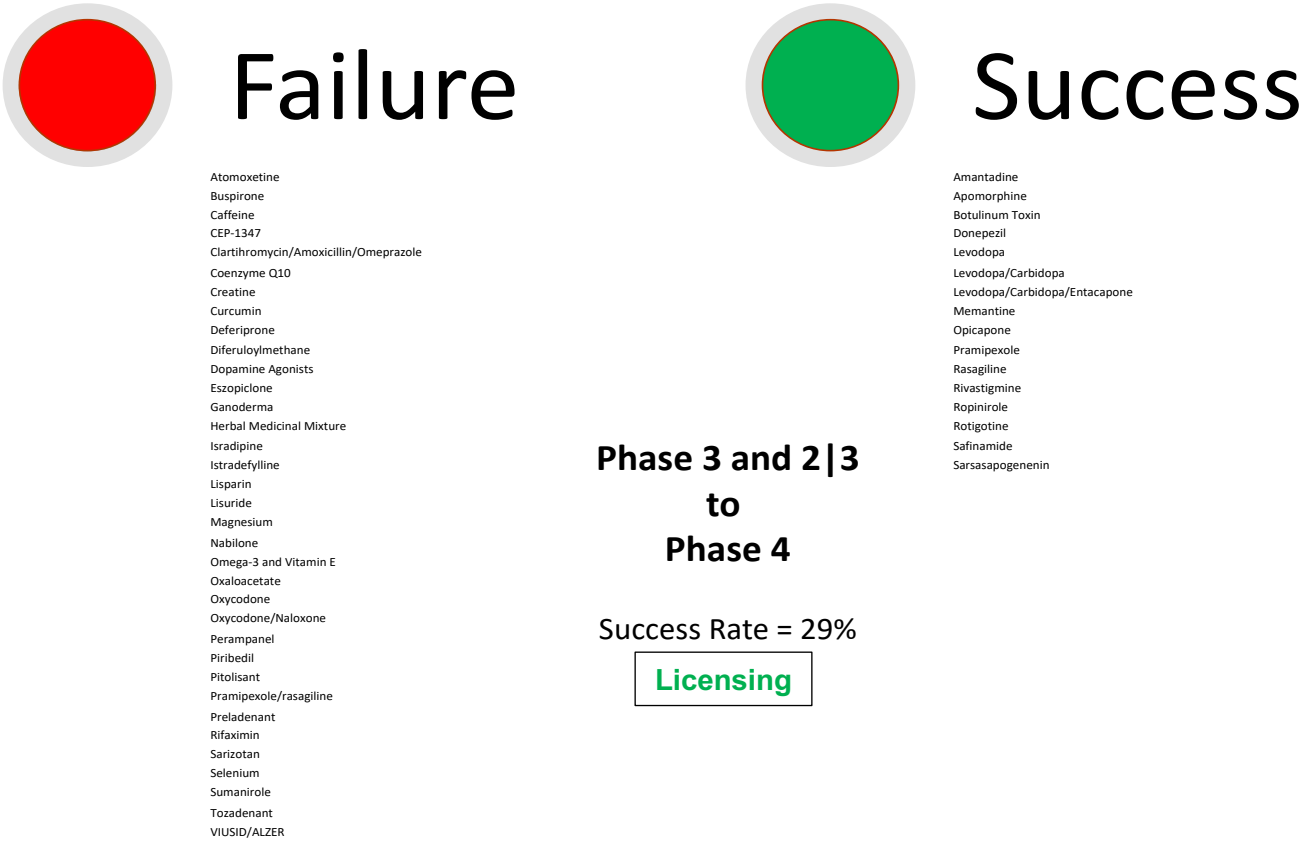


Figure 62. Success Vs. Failure Analysis In Phase 3 And 2|3 To Phase 4
Two columns of list are provided. On the left the compounds that failed to progress to phase 4 (failed licensing). On the right, the compounds that progressed.

Therefore, from phase 3 and 2|3 to phase 4, the following molecules succeeded to advance: Amantadine, Apomorphine, Botulinum Toxin, Donepezil, Levodopa, Levodopa/Carbidopa, Levodopa/Carbidopa/Entacapone, Memantine, Opicapone, Pramipexole, Rasagiline, Rivastigmine, Ropinirole, Rotigotine and Safinamide.

Consequently, from phase 3 and 2|3 to phase 4, the following 35 molecules failed to advance: Atomoxetine, Buspirone, Caffeine, CEP-1347, Clarithromycin/Amoxicillin/Omeprazole, Coenzyme Q10, Creatine, Curcumin, Deferiprone, Diferuloylmethane, Dopamine Agonists, Eszopiclone, Ganoderma, Herbal Medicinal Mixture, Isradipine, Istradefylline, Lisparin, Lisuride, Magnesium, Nabilone, Omega-3 and Vitamin E, Oxaloacetate, Oxycodone, Oxycodone/Naloxone, Perampanel, Piribedil, Pitolisant, Pramipexole/rasagiline, Preladenant, Rifaximin, Sarizotan, Selenium, Sumanirole, Tozadenant and VIUSID/ALZER.

3.4. Regulatory Proof and Licensing Of APIs

In the past 20 years, the following 15 compounds passed phase 3 and thus showed regulatory proof: amantadine, apomorphine, botulinum toxin, donepezil, levodopa, levodopa/carbidopa, levodopa/carbidopa/entacapone, memantine, opicapone, pramipexole, rasagiline, rivastigmine, ropinirole, rotigotine and safinamide. At this stage, these compounds started preregistration to be licensed.

Thus, once phase 3 is complete, the manufacturer files a New Drug Application (NDA). The compounds that pass phase 3, ultimately, are submitted to a New Drug Application (NDA).

NDA is the vehicle through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing. 30% or less of initial drug candidates proceed through the entire multi-year process of drug development, concluding with an approved NDA, if successful. In the case of PD, the success rate was 29%.

Review of the NDA typically lasts one to two years, bringing total drug development and approval to approximately nine years. During the NDA stage, the FDA consults advisory committees made of experts to obtain a broader range of advice on drug safety, effectiveness, and labeling.

Once approved, the drug may be marketed with FDA regulated labeling. The FDA also gathers safety information as the drug is used and adverse events are reported, and it will occasionally request changes in a labeling or will submit press releases as new contraindications arise. If adverse events appear to be systematic and serious, the FDA may withdraw a product from the market.

After NDA process, the 12 following APIs passed postmarketing surveillance for PD: amantadine, apomorphine, carbidopa/levodopa, levodopa, levodopa/carbidopa/entacapone, opicapone, pramipexole, rasagiline, rivastigmine, ropinirole, rotigotine and safinamide.

Donepezil and memantine were licensed as a non-parkinsonian drug class and continued to phase 4 trials for PD dementia associated symptomatology.

Botulinum toxin will eventually fail phase 4 trials, but no reasons or causes for terminating the trial were presented by Allergan Pharmaceutical.

3.5. Analysis Of Success And Failure Rate In T_4 Phase 4 To Postmarketing Surveillance

Initially, only clinical trials in Phase 4 were selected, then a filter was used in study status to include only completed, terminated and withdrawn studies. From the analysis of the PDCard Database, and defining the study status to completed, 29 compounds passed successfully from phase 4 to an adequate postmarketing surveillance. Eight licensed compounds failed to pass PMS. A total number of 35 compounds are present in timepoint T_4.

$$f(\text{success rate}) = f(x) = x / z \Leftrightarrow f(29) = x / 35 \Leftrightarrow \text{success rate} = 83\%$$

$$\delta(\text{failure rate}) = \delta(x) = x / z \Leftrightarrow \delta(6) = x / 35 \Leftrightarrow \text{failure rate} = 17\%$$

In conclusion, and from phase 4 to PMS, the success rate is 83% and the failure rate is 17%.

The molecules that succeeded and failed to advance from phase 4 to PMS are presented in **Figure 63.**

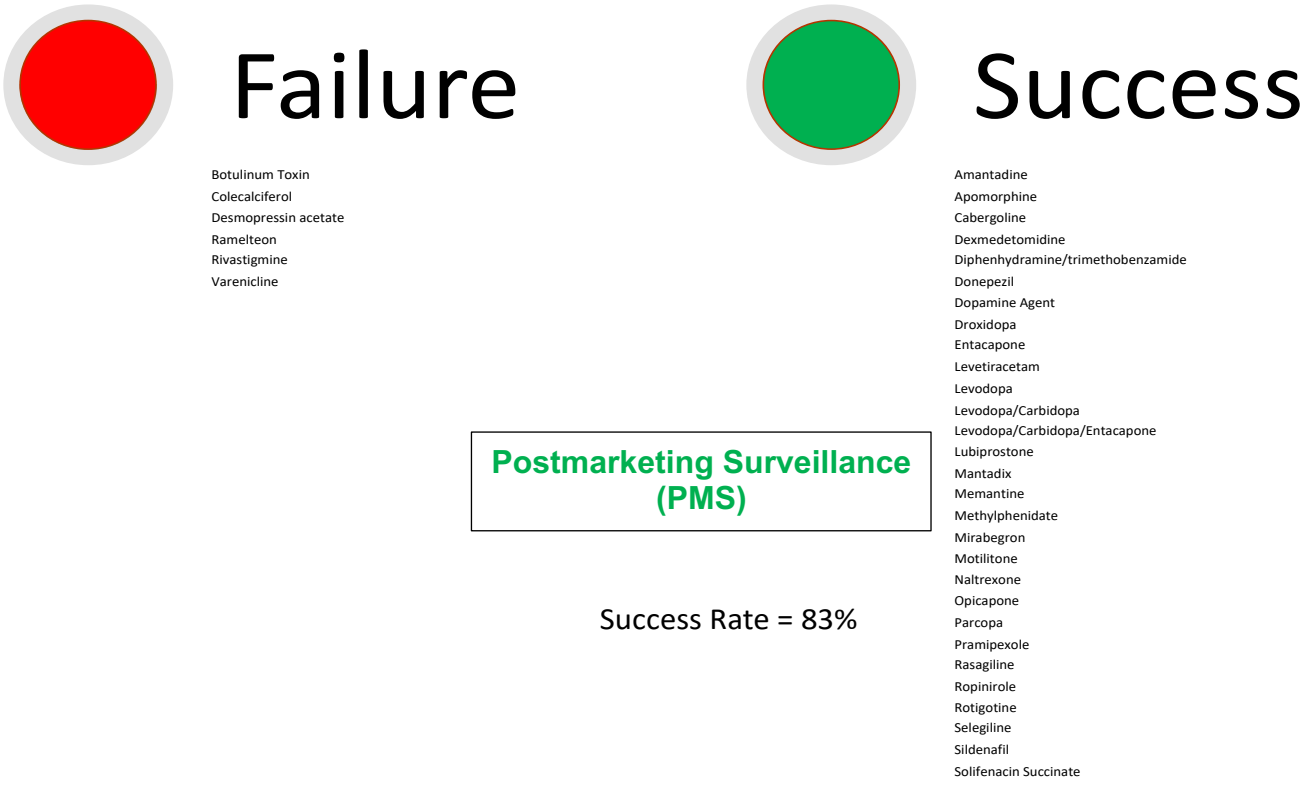


Figure 63. Success Vs. Failure Analysis In Phase 4 (Postmarketing Surveillance) Two columns of list are provided. On the left the compounds that failed PMS. On the right the compounds that received full PMS.

Therefore, the compounds that completed PMS are the following molecules: Amantadine**,** Apomorphine, Cabergoline, Dexmedetomidine, Diphenhydramine/trimethobenzamide, Donepezil, Dopamine Agent, Droxidopa, Entacapone, Levetiracetam, Levodopa, Levodopa/Carbidopa, Levodopa/Carbidopa/Entacapone, Lubiprostone, Mantadix, Memantine,

Methylphenidate, Mirabegron, Motilitone, Naltrexone, Opicapone, Parcopa, Pramipexole, Rasagiline, Ropinirole, Rotigotine, Selegiline, Sildenafil and Solifenacin Succinate.

Consequently, the compounds not completing PMS are the following: Botulinum Toxin, Colecalciferol, Desmopressin acetate, Ramelteon, Rivastigmine and Varenicline.

3.6. Review Of The Success And Failure Rates From T_1 To T_4

The success and failure rates in the 4 different timepoints are presented in **Figure 64.**

T_1 represents the transition from phase 1 to phase 2. T_2 represents the transition from phase 2 and 1|2 to phase 2. T3 represents the transition from phase 3 and 2|3 to phase 4 (licensing). T4 represents the PMS completion.

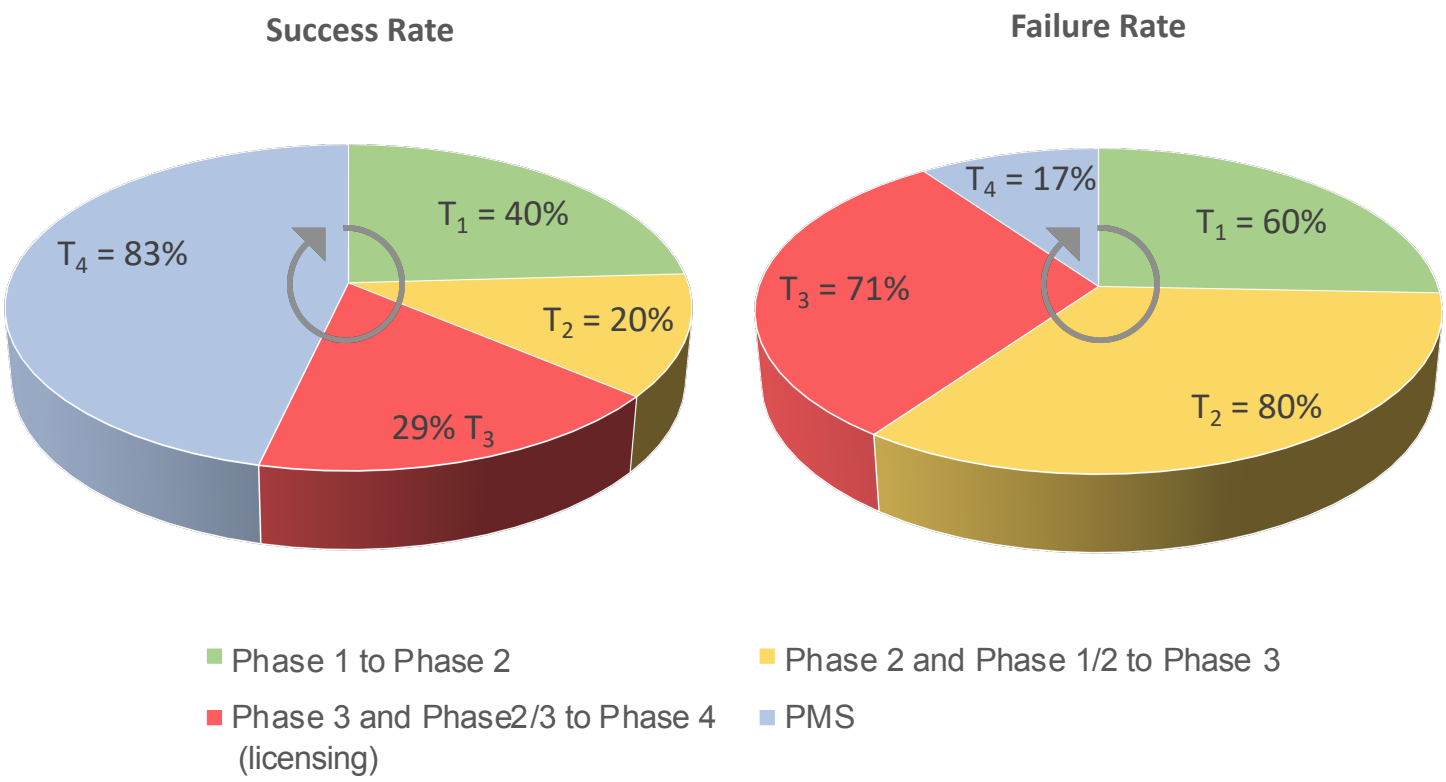


Figure 64. Success Vs. Failure Analysis From Phase 1 To Postmarketing Surveillance
The size of the slices is a correspondent to the percentage of success/failure rate of each timepoint $T_{[1,4]}$.

The success rate in T_1 is equal to 40%, in T_2 is equal to 20%, in T_3 is equal to 29%, and in T_4 is equal to 83%.

The failure rate in T_1 is equal to 60%, in T_2 is equal to 80%, in T_3 is equal to 71%, and in T_4 is equal to 17%.

Henceforth, the success rate is maximum in $T_{4,}$ i.e. in the transition of the API from phase 4, i.e. licensed API, to adequate postmarketing surveillance, and is minimum in $T_{2,}$ i.e. in the transition of the API from phase 2 and 1|2 to phase 3.

Consequently, the failure rate is maximum in $T_{2,}$ i.e. in the transition of the API from phase 2 and 1|2 to phase 3, and minimum in $T_{4,}$ i.e. in the transition of the API from phase 4 (licensed) to PMS completion.

3.7. Clinical Drug Development In PD From 1998 To 2019

PD drug development in the last 20 years produced a significant number of molecules, which were approved marketed compounds that passed confirmatory trials by the regulatory authorities and came into the market. **Figure 65** summarizes the panorama from 1998 to 2019.

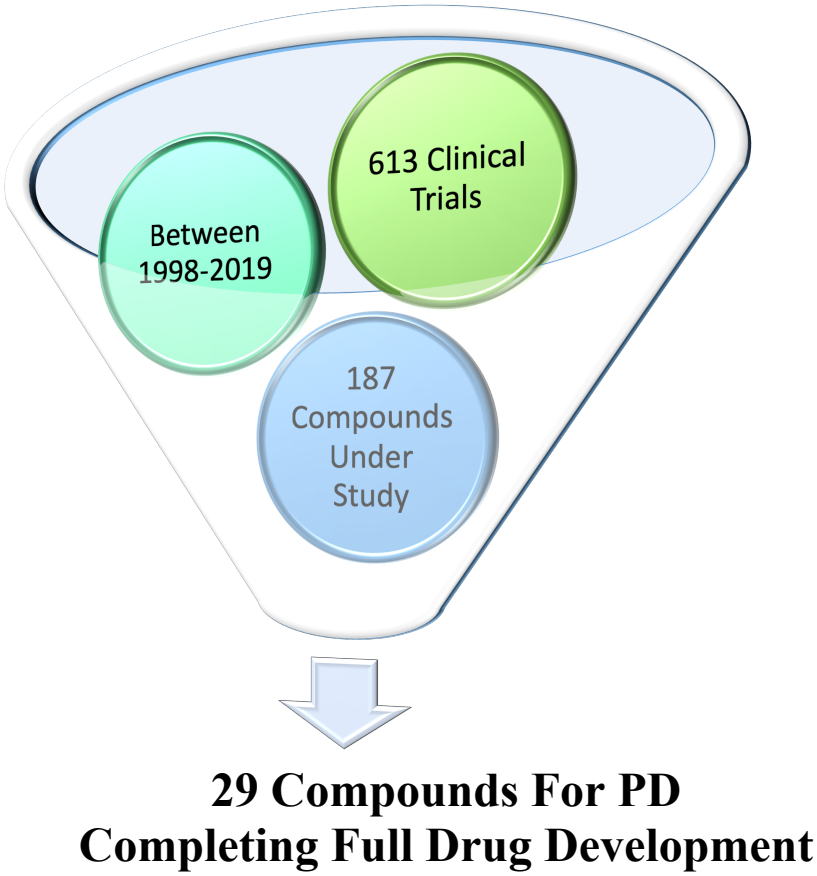


Figure 65. Licensed Compounds For PD In The Last 20 Years
Schematics with the panorama of PD clinical drug development.

Indeed, from 613 clinical trials in PD conducted from 1998 to 2019, 187 compounds were vastly studied. From these 187 molecules, only 29 were considered full approved post-marketed compounds, passing all confirmatory trials, including PMS.

If the same success and failure function are applied here, not for a specific $T_{\alpha,}$ but for the whole period [1998-2019], including all $T_{[1,4]}$, a final f (success rate) and δ (failure rate) are calculated.

Success rate will be calculated accordingly to this function:

$$f(\text{success rate}) = f(x) = x / z,$$

x is equal to the number of compounds that passed successfully in $T_{[1998\text{-}2019]}$
z is equal to total number of compounds in $T_{[1998\text{-}2019]}$

Failure rate will be calculated accordingly to this function:

$$\delta(\text{failure rate}) = \delta(x) = x / z ,$$

x is equal to the number of compounds that failed to advance in $T_{[1998\text{-}2019]}$
z is equal to total number of compounds in $T_{[1998\text{-}2019]}$

An absolute success rate is then:

$$f(\text{success rate}) = f(x) = x / z \Leftrightarrow f(29) = x / 187 \Leftrightarrow \text{success rate} = 16\%$$

An absolute failure rate is then:

$$\delta(\text{failure rate}) = \delta(x) = x / z \Leftrightarrow \delta(158) = x / 187 \Leftrightarrow \text{failure rate} = 84\%$$

3.8. Success And Failure Paths Of The Licensed Postmarket APIs That Passed All Confirmatory Trials, including PMS

An exploratory analysis is conducted in the 29 compounds that received the full licensing and confirmatory postmarketing surveillance by the regulatory authorities, but also in the 8 compounds that failed to pass phase 4.

Different studies were conducted on these 29 compounds that finally led to the adequate PMS.

As shown in **Figure 66,** some compounds were tested in several clinical trials like rasagiline, which had 9 clinical trials, i.e. 15,8% of all the studies conducted in phase 4 (licensed) that led to PMS approval, rotigotine (10,3%), pramipexole (8,8%), ropinirole (7%), levodopa/carbidopa (5,2%) and levodopa/carbidopa/entacapone (5,2%).

While other compounds were tested in less clinical trials like amantadine, droxidopa, opicapone or parcopa, which had only 1 clinical trial each.

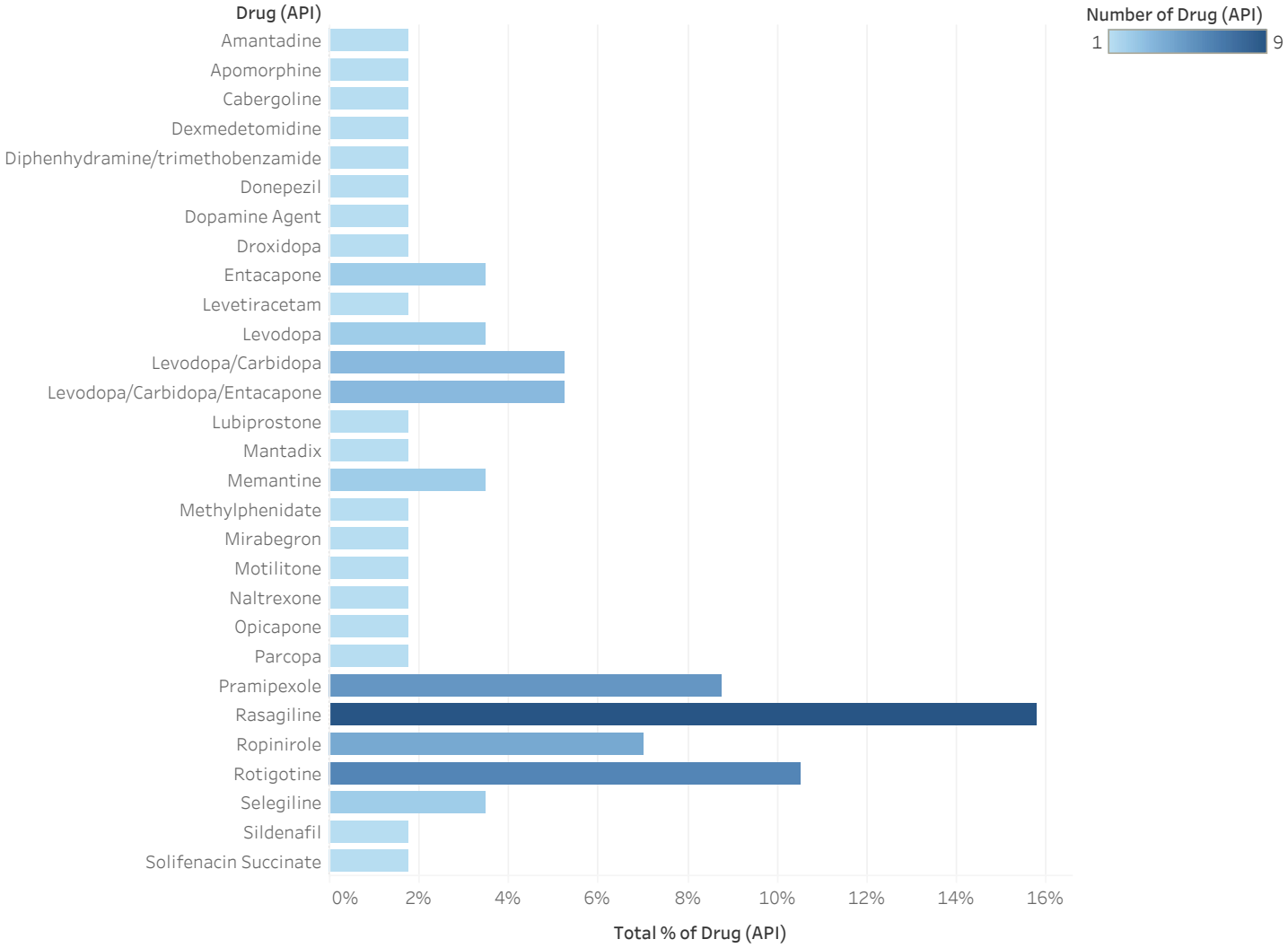


Figure 66. PD Drugs Completing Full Drug Development (Including PMS) Color gradation, from light to dark blue, characterize the number and percentage of the studies conducted for a specific API throughout phase 4 that were studied that success molecule.

To finance these 29 compounds (**Figure 67**), an important funding was provided by different sponsors. API like donepezil were single funded, i.e. by the National Institute of Neurological Disorders and Stroke (NINDS), in one study which corresponded to 1,754% of the total studies that completed full drug development (including PMS) in the last 20 years.

APIs like levodopa were funded by different sponsors, i.e. by the IRCCS San Raffaele, by the Agenzia Italiana del Farmaco, by the University Hospital of Akershus and Solvay Pharmaceuticals, in two studies which corresponded to 3,5% of the total studies that completed full drug development (including PMS) in the last 20 years.

APIs like pramipexole were funded by two big pharma, i.e. by Boehringer Ingelheim and Sandoz, in two separate studies which corresponded to 7,018% and 1,754%, respectively, of the total studies that completed full drug development (including PMS) in the last 20 years.

Conclusively, Boehringer Ingelheim, Sandoz and GlaxoSmithKline were the big pharma that conducted more studies for the effective approval and adequate postmarketing surveillance of the licensed molecules in phase 4.

Drug (API)	Sponsor/Collaborators
Amantadine	Seoul National University Boramae Hospital
Apomorphine	US WorldMeds LLC
Cabergoline	Technische University ot Dresden|Pfizer
Dexmedetomidine	Diskapi Teaching and Research Hospital
Diphenhydramine/trimethobenzamide	Ipsen|INC Research Limited
Donepezil	National Institute of Neurological Disorders and Stroke (NINDS)
Dopamine Agent	I.R.C.C.S. Fondazione Santa Lucia
Droxidopa	Vanderbilt University Medical Center
Entacapone	Assistance Publique - Hopitaux de Paris
	Orion Corporation, Orion Pharma
Levetiracetam	UCB Pharma GmbH
Levodopa	IRCCS San Raffaele|Agenzia Italiana del Farmaco
	University Hospital, Akershus|Solvay Pharmaceuticals
Levodopa/Carbidopa	Sandoz
	Swedish Society for Medical Research
Levodopa/Carbidopa/Entacapone	Novartis
	Orion Corporation, Orion Pharma
Lubiprostone	Baylor College of Medicine|University of South Florida
Mantadix	University Hospital, Toulouse
Memantine	Baylor College of Medicine|Forest Laboratories
	University Hospital, Lille
Methylphenidate	University of Cincinnati|Michael J. Fox Foundation for Parkinson's Research
Mirabegron	Daniel Burdick, MD|Astellas Pharma US, Inc.|Burdick, Daniel, M.D.
Motilitone	Seoul National University Hospital
Naltrexone	University of Pennsylvania|Michael J. Fox Foundation for Parkinson's Research
Opicapone	Bial - Portela C S.A.
Parcopa	Baylor College of Medicine|UCB Pharma
Pramipexole	Boehringer Ingelheim
	Sandoz
Rasagiline	Brown University|Teva Pharmaceuticals USA
	Georgetown University|Teva Neuroscience, Inc.
	Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau
	Technische University of Dresden
	Teva Branded Pharmaceutical Products, R&D Inc.|Teva Pharmaceutical Industries
	Teva Neuroscience, Inc.|H. Lundbeck A/S|Teva Pharmaceutical Industries
	Teva Neuroscience, Inc.|Teva Pharmaceutical Industries
	Teva Pharmaceutical Industries
	University of Florida
Ropinirole	GlaxoSmithKline
	Seoul National University Hospital
Rotigotine	Otsuka Pharmaceutical Co., Ltd.
	UCB BIOSCIENCES GmbH|UCB Pharma
	UCB Korea Co., Ltd.|UCB Pharma
	UCB Pharma
Selegiline	Baylor College of Medicine
	Parkinson's Disease and Movement Disorder Center of Boca Raton
Sildenafil	Bispebjerg Hospital
Solifenacin Succinate	University of South Florida

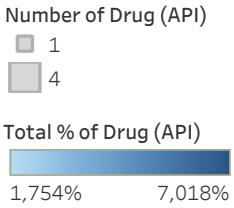


Figure 67. PD Drugs Completing Full Drug Development (Including PMS) Sorted By Sponsor
Relative % of the total 29 postmarket compounds that passed confirmatory trials is presented.
The size of the square and the gradient of blue is a correspondent to the number of clinical trials for each API.

Indeed, industry has funded more studies for each API approved individually when compared to non-industry sponsors. **Figure 68** shows a summary of the compounds that were approved with industry funds and non-industry sponsors.

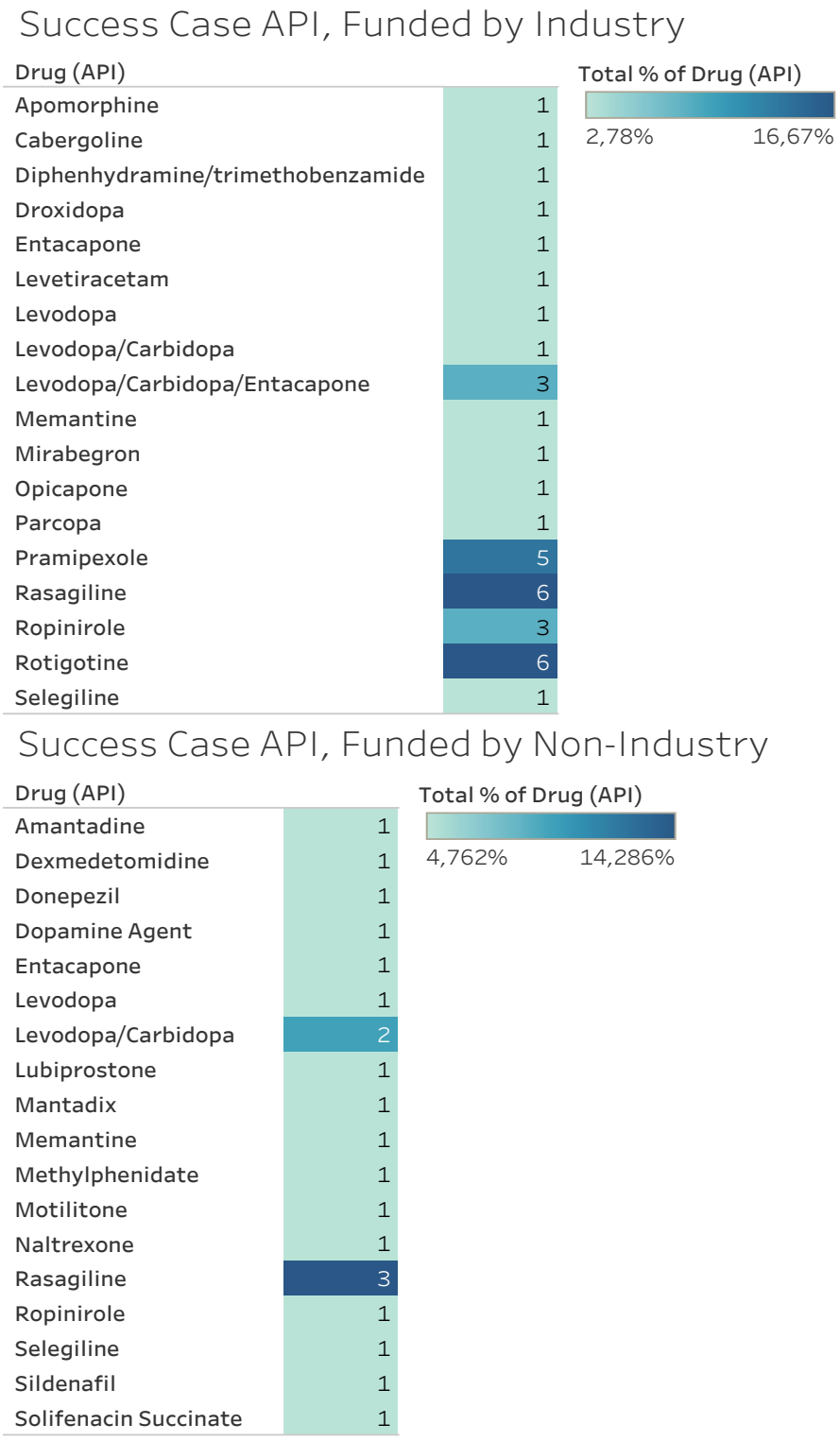


Figure 68. PD Drugs Completing Full Drug Development (Including PMS) Funded By Industry And Non-Industry
Relative % of the total 29 postmarket compounds that passed confirmatory trials, sponsored by industry and non-industry funds.

In the last 20 years, industry has funded 36 studies in phase 4, which conducted to the full marketing (including PMS) of 18 molecules. Whilst, 21 studies were conducted by non-industry sponsors, which led to the full marketing (including PMS) of 18 compounds. Rasagiline was the compound that was more studies by both types of sponsors.

From all the 29 compounds that were tested, 12 were considered new molecular entities. **Figure 69** shows the APIs that fully entered the market, after PMS, of PD drug development in the past 20 years. The molecular entities that were more studied were rasagiline (30,77%), followed by rotigotine, ropinirole and pramipexole.

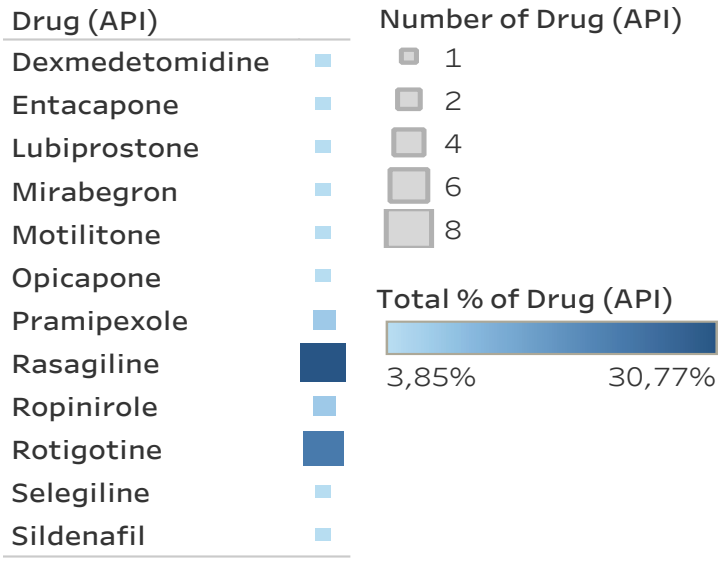


Figure 69. PD Drugs Completing Full Drug Development (Including PMS) Sorted By New Molecular Entity
The size and the gradient of blue correspond to the relative % of studies conducted by each APIs considered new molecular entities.

As previously referred in the Introduction, PD drug development is known as non-informative, but mainly in early-stage trials. Indeed, this tendency is also observed in phase 4, but with less impact. Studies that published results (**Figure 70**) correspond to 40,35%, while 59,65% did not publish any results in phase 4.

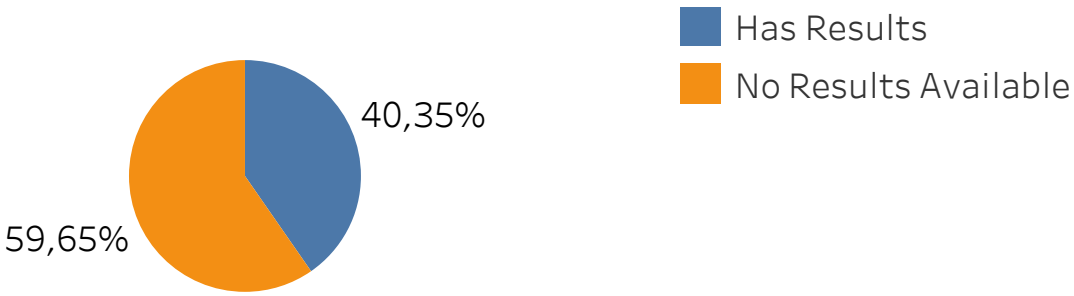


Figure 70. Postmarketing Surveillance By Study Results
The size of the slice is a correspondent to the relative % of clinical trials that presented results in phase 4.

From all the 29 compounds passing PMS (**Figure 71**), 75,44% were tested in a sample of subjects with all stages of PD. Those were the more effective studies, producing more approved postmarket surveillance compounds.

However, clinical trials that were conducted in early-stage PD led to 10,53% of the approved entities and that were conducted in advanced-stage PD led to 12,28% of compounds.

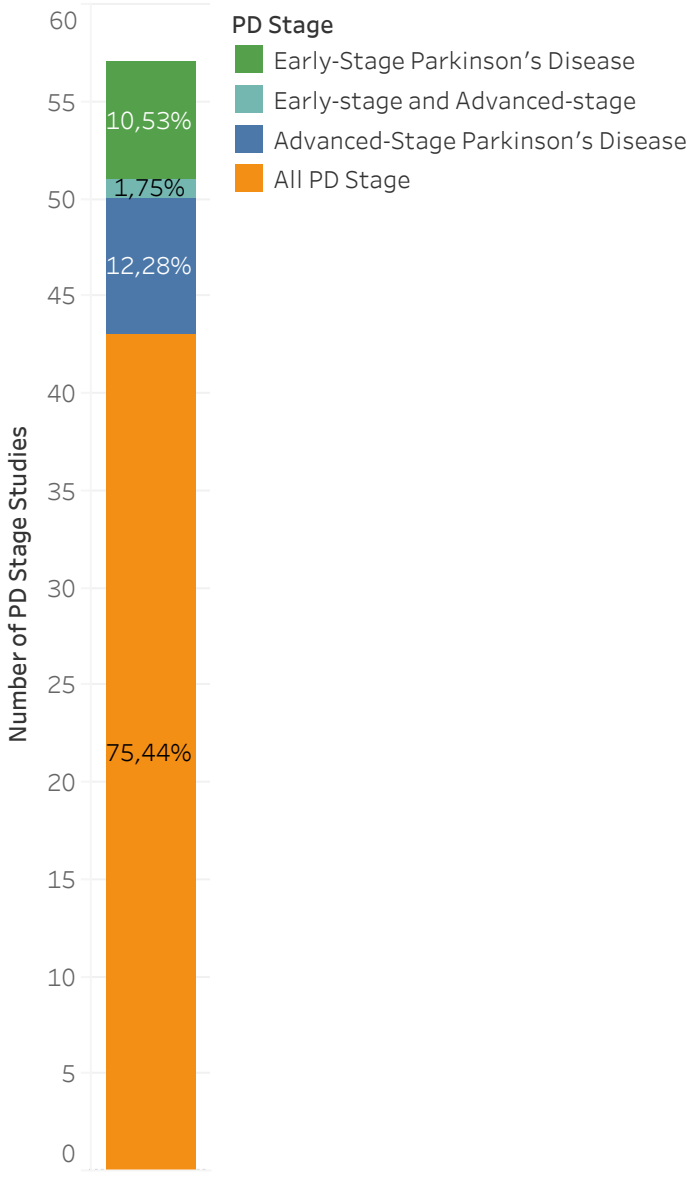


Figure 71. PD Stage On Postmarketing Surveillance Trials
A stacked plot is presented with the relative % of studies in phase 4 that completed full development program, and sorted by the stage of PD of the subjects.

Another factor of success was the type of masking used (**Figure 72**).

Clinical trials that used quadruple blinding (47,22%) are the ones that produced more licensed and postmarket compounds, followed by double blinding (38,89%), in the last 20 years of PD clinical drug development.

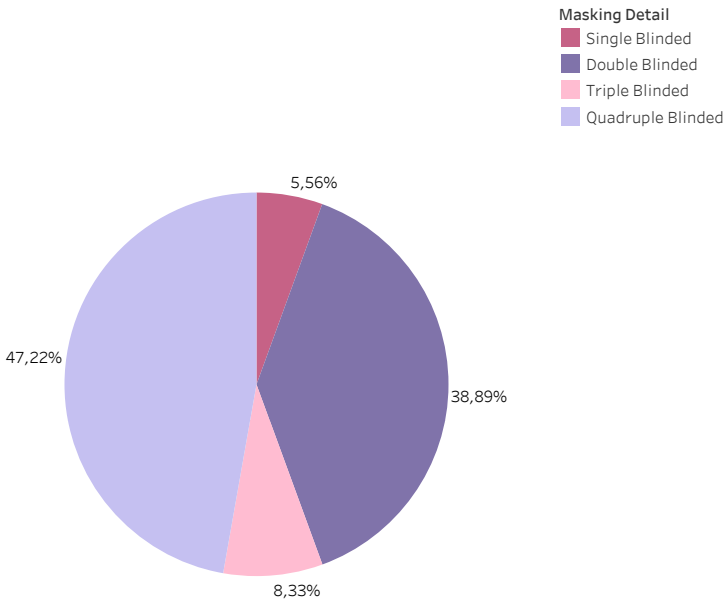


Figure 72. PD Drugs Completing Full Drug Development (Including PMS) By Masking Type On Blinded Studies
The relative % of PMS studies
that used single, double, triple and quadruple blind is presented.

Likewise, the type of design used is also a cause of success or failure. Indeed, as shown in **Figure 73**, the parallel assignment (59,65%) was the type of design that produced more licensed and postmarket compounds, followed by single group assignment (26,32%) and crossover assignment (12,28%).

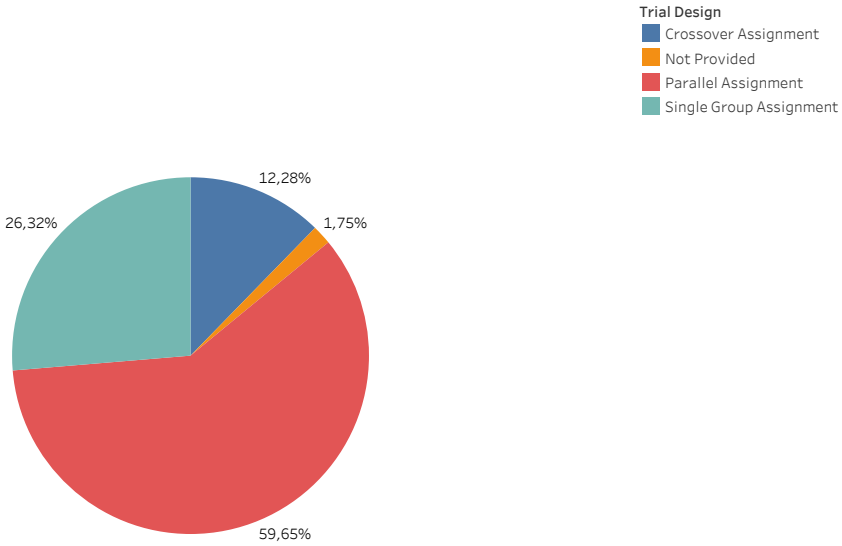


Figure 73. Postmarketing Surveillance Studies By Trial Design
The relative % of Phase 4 studies that used crossover,
parallel and single group assignment is presented.

Other identified cause of success in PD drug development was related to drug administration. **Figure 74** shows the analysis of the drug administration route, the drug formulation type and the administration type. The studies that used oral (76,79%) as a

preferred route of administration for licensed compounds, followed by transdermal (10,71%), and tailed by intraduodenal and intravenous, with 5,36% each.

The studies that used tablets (76,79%) as a preferred drug formulation licensed compounds, followed by patch (10,71%), and tailed by gel and solution, with 5,36% each. The studies that used solid units (76,79%) as a preferred administration type licensed compounds, followed by infusion (16,07%), and tailed by injection, with 5,36%.

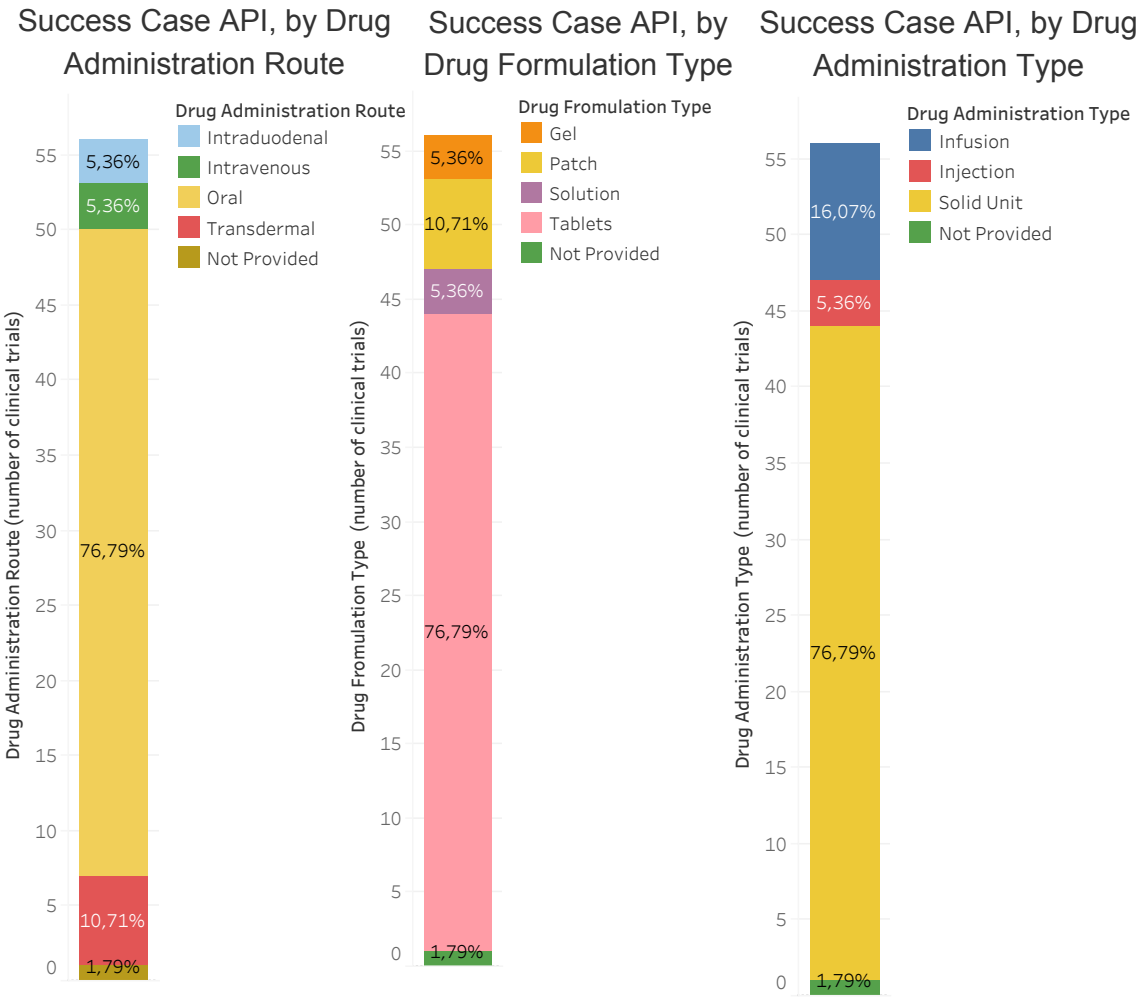


Figure 74. PMS Studies By Drug Administration Route, Drug Formulation Type And Administration Type
A stacked plot is presented with the relative % of studies in phase 4 that completed the full developmental program and sorted by drug administration.

The 29 compounds that completed the full developmental program and that passed confirmatory trials have different drug modulation mechanisms. **Figure 75** shows only the principal drug mechanisms. Dopamine receptor modulators, like pure levodopa and levodopa combinations, represent 52,63% of the success path in the last 20 years. In second, monoamine oxidase modulators (19,30%), like selegiline and rasagiline, were tested in PD drug development. Thirdly, adrenergic receptor modulators (5,26%), like droxidopa and mirabegron, and catechol o-methyltransferase modulators (5,26%), like entacapone and opicapone, were licensed compounds that passed confirmatory trials by the regulatory authorities.

Principal Drug Modulation Mechanism	
Acetylcholinesterase Modulators	1,75%
Adrenergic Receptors Modulators	5,26%
Catechol O-Methyltransferase Modulators	5,26%
Chloride Channel Modulators	1,75%
Dopamine Receptors Modulators	52,63%
Histamine Receptors Modulators	1,75%
Monoamine Oxidase Modulators	19,30%
Motilin Modulators	1,75%
Muscarinic Receptors Modulators	1,75%
Nicotinic Receptor Modulators	3,51%
Opioid Receptors Modulators	1,75%
Phosphodiesterase Modulators	1,75%
SV2A Protein Modulators	1,75%

Principal Drug Modulat.
1 30

Figure 75. Success Case APIs, By Principal Drug Modulation Mechanism
Relative % of the total principal drug modulation mechanisms of the 29 licensed compounds.

Finally, the 29 licensed compounds were tested with drug and target-related markers. **Figure 76** reviews the biomarkers that were used.

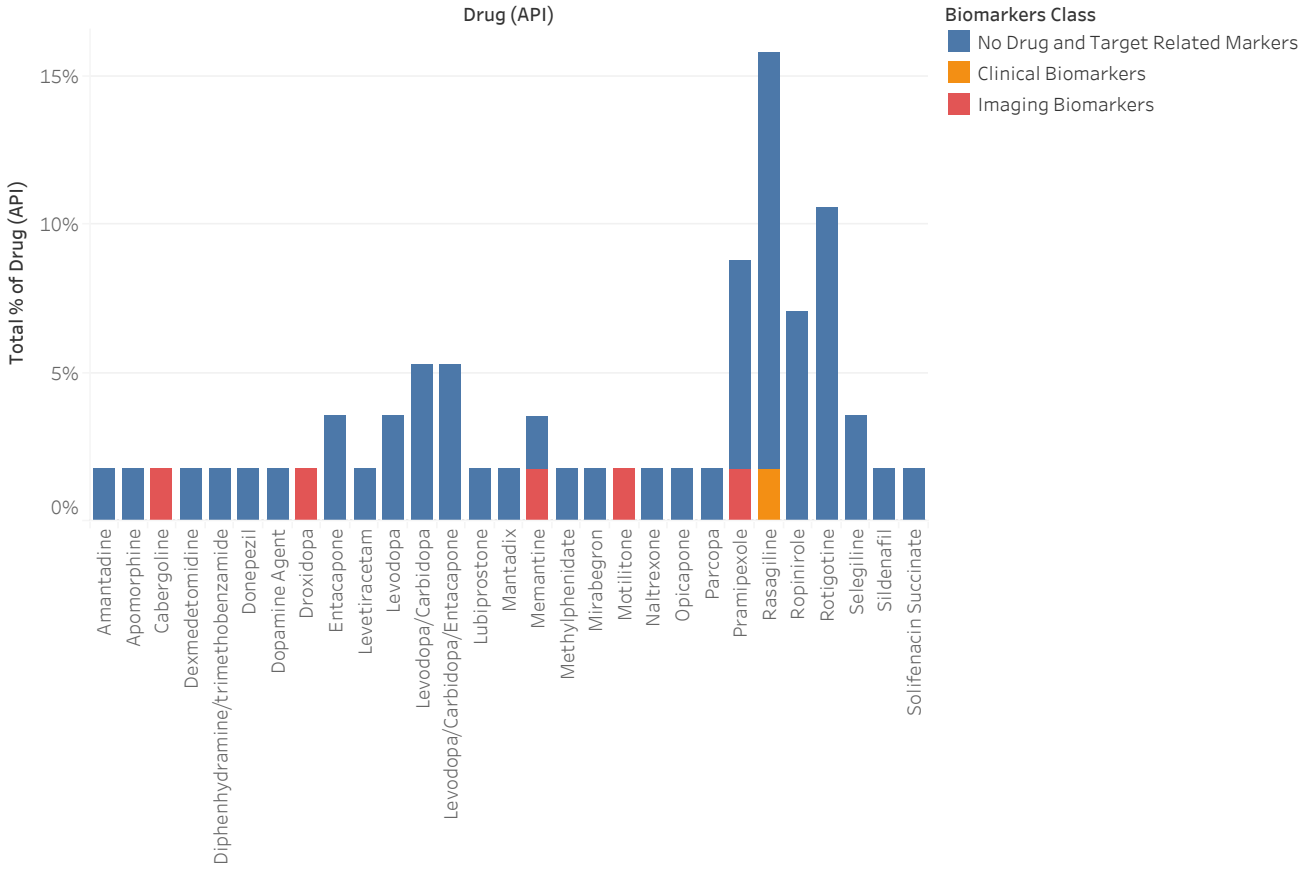


Figure 76. Licensed Drugs Passing PMS Sorted By Biomarker Class
The relative % of studies using the two types of biomarkers (clinical and imaging) are represented in a stack plot.

Henceforth, the majority of studies conducting to licensing and completing postmarketing surveillance have not used drug and target-related markers.

Cabergoline, droxidopa, memantine, motilitone and pramipexole used imaging biomarkers. For instance, droxidopa used fMRI to monitor the effects of norepinephrine-targeted therapy for action control in PD; pramipexole used Emission Computed Tomography (SPECT) to study the percentage change from the baseline in the striatum uptake of dopamine followed by pramipexole administration.

Rasagiline rather used clinical biomarkers, specifically polysomnography to monitor the quality of sleep in PD subjects.

4. Success And Failure Rate Of The Antiparkinsonians Specific Drug Class

From the 29 licensed compounds that passed all confirmatory trials, 26,32% of the studies conducted were for non-parkinsonians drugs, while 73,68% of the studies conducted were for antiparkinsonians. **Figure 77** shows a higher success rate for compounds that were specifically designed to treat PD symptoms.

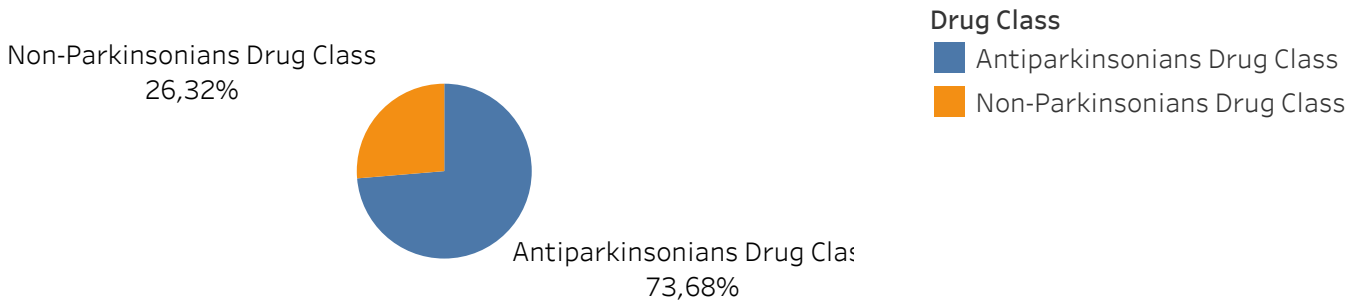


Figure 77. Studies of Licensed Drugs With NDA Approval Sorted by Class The dimension of the slice is a correspondent to the relative % of APIs that belong to Antiparkinsonians or Non-Parkinsonians drugs.

Those 29 licensed compounds have passed from NDA submission to NDA approval, and are divided in two classes: Antiparkinsonian drug class or agents and Non-Parkinsonian drug class.

Antiparkinsonian agents are licensed compounds specifically developed and designed for the treatment of PD. Their aim is to replace dopamine either by drugs that release dopamine or those that mimic the action of dopamine. Parkinson's disease is a degenerative disorder of movement that occurs due to dopamine deficiency in the basal ganglia. Antiparkinsonian agents attempt to replace dopamine and treat or halt the symptoms such as tremor, hypokinesia, and so on.

Non-Parkinsonian drugs are licensed compounds developed and designed for the treatment other medical conditions and used in PD associated symptomatology and the management of the numerous non-motor and sensory manifestations.

The 15 antiparkinsonians licensed compounds present in PDCard Database are the following: amantadine, apomorphine, dopamine agent, entacapone, levodopa, carbidopa/levodopa, levodopa/carbidopa/entacapone, mantadix, opicapone, parcopa, pramipexole, rasagiline, ropinirole, rotigotine and selegiline.

The 14 non-Parkinsonian licensed compounds present in PDCard Database are the following: Cabergoline, Dexmedetomidine, Diphenhydramine/trimethobenzamide, Donepezil, Droxidopa, Levetiracetam, Lubiprostone, Memantine, Methylphenidate, Mirabegron, Motilitone, Naltrexone, Sildenafil and Solifenacin Succinate. These 14 non-Parkinsonian will not be used to calculate the final success and failure rate.

From the 15 antiparkinsonians licensed compounds, passing PMS, the following 10 compounds were already successfully preregistered for PD after regulatory proof: amantadine, apomorphine, carbidopa/levodopa, levodopa, levodopa/carbidopa/entacapone, opicapone, pramipexole, rasagiline, ropinirole and rotigotine. They received full NDA approval and regulatory license to marketing and they completed successfully postmarketing surveillance studies.

Moreover, safinamide was already preregistered for PD after receiving regulatory proof, and received full NDA approval and regulatory license to marketing. However, safinamide did not undergo yet postmarketing surveillance studies.

Likewise, rivastigmine was already preregistered for PD after receiving regulatory proof, and received full NDA approval and regulatory license to marketing. However, rivastigmine was admitted to two postmarketing surveillance studies. One was terminated because the enrollment and funds were insufficient. Another phase 4 trial started in 2019 and is in recruitment status. The trial is monocentered, to be more cost-effective, and is expected to finish in April 2020.

Selegiline, in August 2008, and Entacapone, in November 2009, received full NDA approval and regulatory licensing to market while already in final phase 4 postmarketing surveillance completion.

The following three antiparkinsonians had a similar success path but will not be included for the final success and failure rate of antiparkinsonian agents. Dopamine agent is not a specified API and thus will not be used for the final success rate of antiparkinsonian agents. Mantadix APIs is amantadine, and Parcopa APIs is carbidopa/levodopa, and thus already included in 13 antiparkinsonian agents finishing the complete development program.

Finally, from the 613 clinical trials in PD conducted from 1998 to August 2019 and the 187 compounds only 14 APIs were finally licensed antiparkinsonians agents passing the complete development program. These were the Amantadine, the Apomorphine Hydrochloride, the Carbidopa/Levodopa, the Entacapone, the Levodopa, the Levodopa/Carbidopa/Entacapone, the Opicapone, the Pramipexole, the Rasagiline, the Rivastigmine Tartare, the Ropinirole Hydrochloride, the Rotigotine, the Safinamide and the Selegiline. Then the same success and failure function is applied here, not for all drug classes but only for antiparkinsonian agents between 1998 and 2019.

Success rates will be calculated accordingly to this function:

$$f(\text{success rate}) = f(\text{x}) = \text{x} / \text{z} ,$$

x is equal to the number of antiparkinsonians that passed successfully in $T_{[1998\text{-}2019]}$
z is equal to total number of total compounds in $T_{[1998\text{-}2019]}$

Failure rates will be calculated accordingly to this function:

$$\delta \text{ (failure rate)} = \delta(x) = x / z \text{ ,}$$

x is equal to the number of compounds that failed to advance in $T_{[1998\text{-}2019]}$
z is equal to total number of compounds in $T_{[1998\text{-}2019]}$

An antiparkinsonian success rate is then:

$$f \text{ (success rate)} = f(x) = x / z \Leftrightarrow f(14) = x / 187 \Leftrightarrow \text{success rate} = 7\%$$

An antiparkinsonian failure rate is then:

$$\delta \text{ (failure rate)} = \delta(x) = x / z \Leftrightarrow \delta(173) = x / 187 \Leftrightarrow \text{failure rate} = 93\%$$

4.1. Phase 4: Postmarket APIs That Passed All Confirmatory Trials

As a conclusion, a final chapter of results is presented with a review of the 14 licensed antiparkinsonian agents. Those agents, extracted from PCCard, were confirmed licensed FDA compounds, from www.centerwatch.com, the trusted source for clinical trials information (last update 02.08.2020).

In the past 20 years, 14 different antiparkinsonian agents have successfully completed the full developmental program, including PMS, and were licensed and approved for PD. Those 14 different antiparkinsonian agents were marketed (**Figure 78**) by 16 different sponsors, and in 20 different formulations.

Drug Name	Comercial Name	Approval Year	Company Name
Amantadine	Symmetrel	2003	Endo Pharmaceuticals
	Gocovri	2017	Adamas Pharmaceuticals
	Osmolex	2018	Osmotica Pharmaceutical
Apomorphine Hydrochloride	Apokyn	2004	Mylan Laboratories
	Kynmobi	2020	Sunovion Pharmaceuticals
Carbidopa and Levodopa	Parcopa	2004	Schwarz Pharma
	Duopa	2015	AbbVie
	Rytary	2015	Impax Laboratories
Entacapone	Comtan	1999	Novartis
Levodopa	Inbrija	2018	Acorda Therapeutics
Levodopa, Carbidopa, Entocapone	Stalevo	2003	Novartis
Opicapone	Ongentys	2020	Neurocrine Biosciences
Pramipexole	Mirapex	1997	Pharmacia & Upjohn, Boehringer Ingelheim
Rasagiline	Azilect	2006	Teva Pharmaceuticals
Rivastigmine Tartrate	Exelon	2007	Novartis
Ropinirole Hydrochloride	Requip	1997	SmithKline Beecham
Rotigotine	Neupro	2007	Schwarz Pharma
Safinamide	Xadago	2017	Newron Pharmaceuticals
Selegiline	Selegiline	1997	Teva Pharmaceuticals
	Zelapar	2006	Valeant

Figure 78. Licensed Molecules, Commercial Names, FDA Approval Year And Company Name
The name of the sponsor and commercial name per API is presented.

Novartis was one of the big pharma licensing more compounds (Exelon®, Rivastigmine Tartrate; Comtan®, Entacapone; Stalevo®, levodopa/carbidopa/entacapone).

Indeed, as shown in **Figure 79**, the successful paths started in 1997, the year that selegiline, Requip® (ropinirole hydrochloride) and Mirapex® (pramipexole) were licensed.

Selegiline has been approved for the treatment of PD. Selegiline is a generic equivalent of Somerset's Eldepryl tablets, a drug for the treatment of PD. Other generic versions of this product have been introduced over the last several months.

Mirapex® (pramipexole) is the first Parkinson's agent approved by the FDA since Somerset's monoamine oxidase inhibitor Eldepryl in 1989. It was approved for the treatment of the signs and symptoms of idiopathic PD and can be used to treat all stages of PD. When given concomitantly with levodopa, improves patients with advanced PD and levodopa-induced motor fluctuations.

Requip® (ropinirole hydrochloride) is licensed for use in patients with early PD and in patients with advanced Parkinson's disease.

In 1999, Comtan® (entacapone) was licensed for the management of idiopathic PD helps prolonging the effects of the levodopa/carbidopa preparations, such as improved motor performance and increased amounts of "on" time (periods of good function and mobility in which a patient is able to perform common daily activities such as walking, speaking, and writing).

In 2003, Stalevo® (levodopa/carbidopa/entacapone) was licensed for the treatment of PD patients with end-of-dose motor fluctuations not stabilized on levodopa/dopa decarboxylase inhibitor treatment.

Also in 2003, Symmetrel® (amantadine) was licensed for the treatment of dyskinesia and involuntary movements in patients with early-stage PD.

In 2004, Apokyn® (apomorphine hydrochloride) was licensed to treat acute and intermittent hypomobility, i.e. the "off" episodes associated with advanced Parkinson's disease, as adjunct therapy to standard levodopa therapy.

Also in 2004, Parkopa® (carbidopa/levodopa) was licensed for the treatment of shakiness, stiffness and difficulties in locomotion associated with idiopathic PD.

In 2006, Azilect® (rasagiline) was licensed for the treatment of idiopathic PD as monotherapy, or as an adjunctive treatment to levodopa in patients with end of dose fluctuations.

In 2006, Zelapar® (selegiline) was licensed as an add-on therapy to management of on-off symptoms and end-dose fluctuations in PD.

In 2007, Neupro® (rotigotine) was licensed for the treatment of the signs and symptoms of early-stage idiopathic PD.

Also in 2007, Exelon® (rivastigmine tartrate) was licensed for the treatment of mild to moderate dementia associated with PD.

In 2015, Duopa® (carbidopa/levodopa) was licensed for the treatment of motor fluctuations in patients with advanced Parkinson's disease.

Also in 2015, Rytary (carbidopa/levodopa) was licensed for the treatment of post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

In 2017, Gocovri® (amantadine) was licensed for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications.

Also in 2017, Xadago® (safinamide) was licensed to as an adjunctive treatment to levodopa/carbidopa in PD patients with "off" episodes.

In 2018, Osmolex® (amantadine) was licensed for the treatment of drug-induced extrapyramidal reactions in PD.

Also in 2018, Inbrija (levodopa) was licensed to treat symptoms of PD during the off-episodes.

Finally, in 2020, Ongentys® (opicapone) was licensed for the adjunctive treatment to levodopa/carbidopa in PD patients with "off" episodes.

Also in 2020, Kynmobi® (apomorphine hydrochloride) was licensed for the treatment of acute and intermittent "off" episodes.

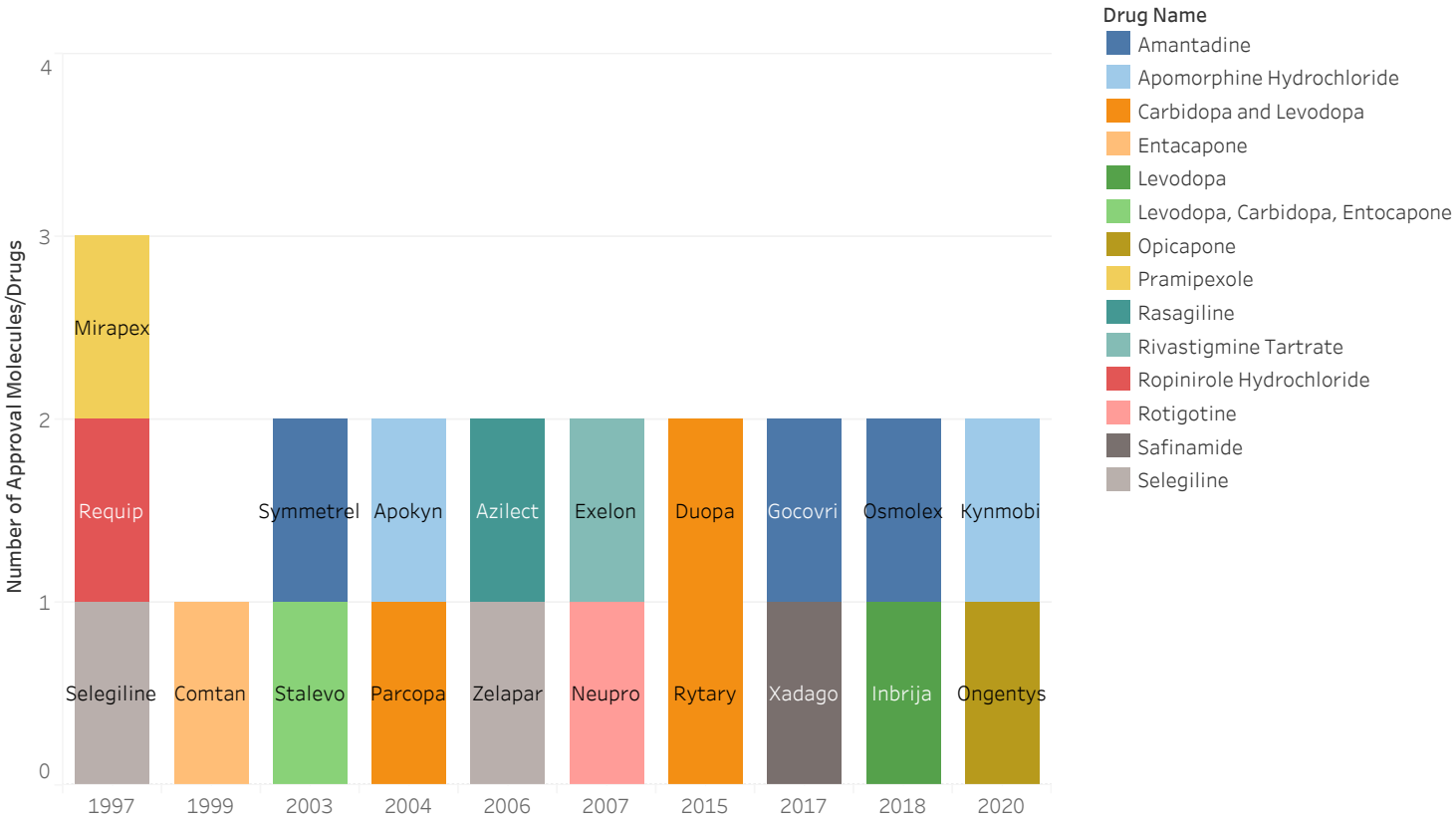


Figure 79. Licensed Molecules And Commercial Names Sorted By FDA Approval Year
Each color represents the name of the compounds that are approved by FDA.
X-axis represent the approval FDA year. The name of commercial drug is specified on the graph.
The number of APIs per year is presented.

4.2. Incomplete Drug Development Program: Causes For Failing An API In Phase 3 And Phase 4

Concluding, and after fully exploring the success paths, the failure paths are then addressed. In the last 20 years, several reasons were presented for not progressing an API to complete licensing and adequate postmarketing surveillance.

The 35 compounds that failed to succeed phase 3, i.e. licensing, (**Figure 80)** and the 6 compounds that failed to succeed phase 4. i.e. PMS, **(Figure 81)** were due to the following reasons.

In phase 3 and for the 35 compounds that failed to succeed phase 3, i.e. licensing, lack of efficacy (15%) was the main reason for terminating a study. Secondly,

decision to change the study design (10%) and new safety information (10%) were the causes for terminating phase 3 trials. Thirdly, all with 5%, the reasons were the following : additional long-term safety data no longer needed, business reasons, change in sponsorship, company decision to return all rights for other sponsors, due to clinical trial supplies shortage, futility, lack of recruitment, low enrollment and unlikely to provide evidence of significant effect.

However, some studies that failed to receive regulatory proof (15%) do not publish the reasons for terminating or withdrawing the clinical trial.

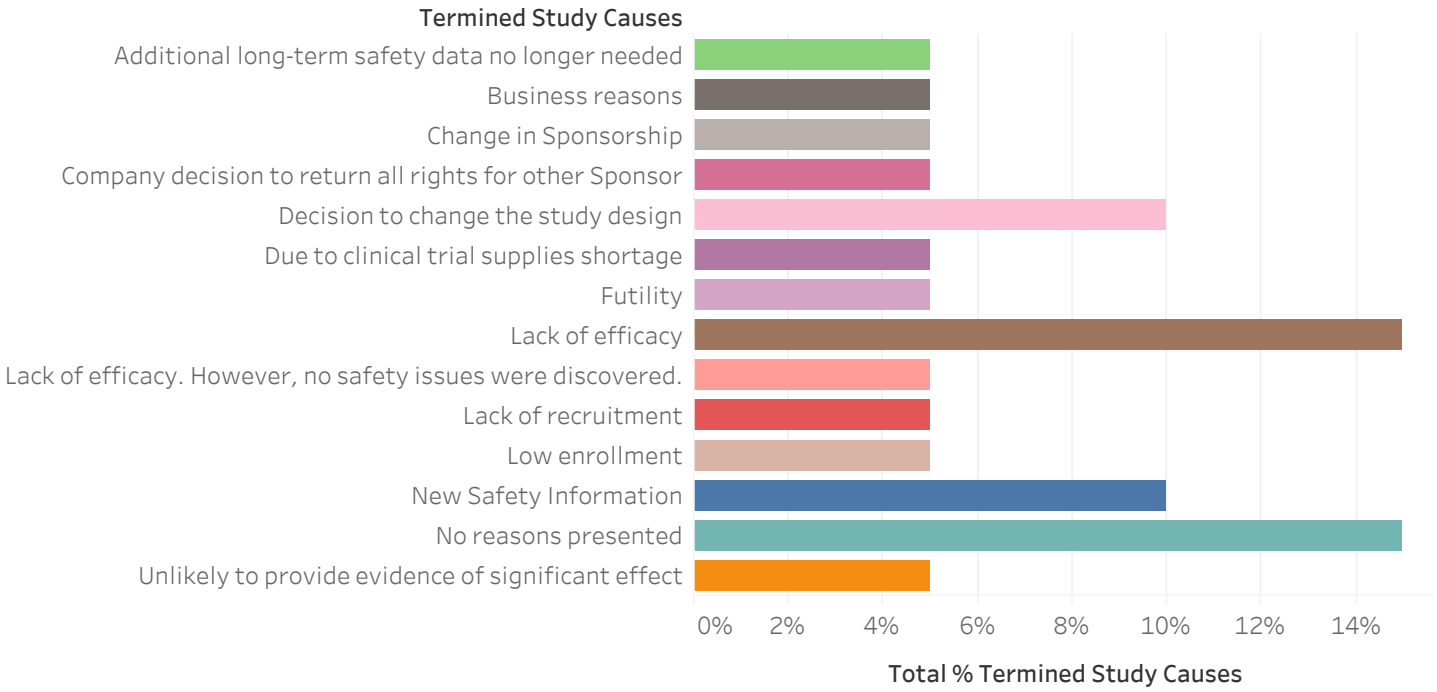


Figure 80. Failure Causes On 3th Phase Of Development Trials
Each color represents a reason for failing regulatory proof.
The total % studies terminating by the causes listed are presented.

In phase 4 and for the 6 compounds that failed to succeed phase 4, i.e. PMS, the majority of studies that failed confirmatory trials (34%) do not publish the reasons for terminating or withdrawing the clinical trial.

The studies that presented reasons of falling are the following (7% of the total terminated or withdrawn studies for each reason):

(i) business decision brand strategy; no patients enrolled;

(ii) enrollment to slow, insufficient funds; (

(iii) inadequate enrollment, protocol too challenging for participants, lack of observable benefit after analysis of patients;

(iv) insufficient patient enrollment, insufficient funds for completion;

(v) lack of recruitment;

(vi) payments stopped by grant provider;

(vii) slow enrollment;

(viii) slow recruiting;

(ix) study withdrawn due to personnel limitations;

(x) study withdrawn with intent of pursuing larger, multi-site study.

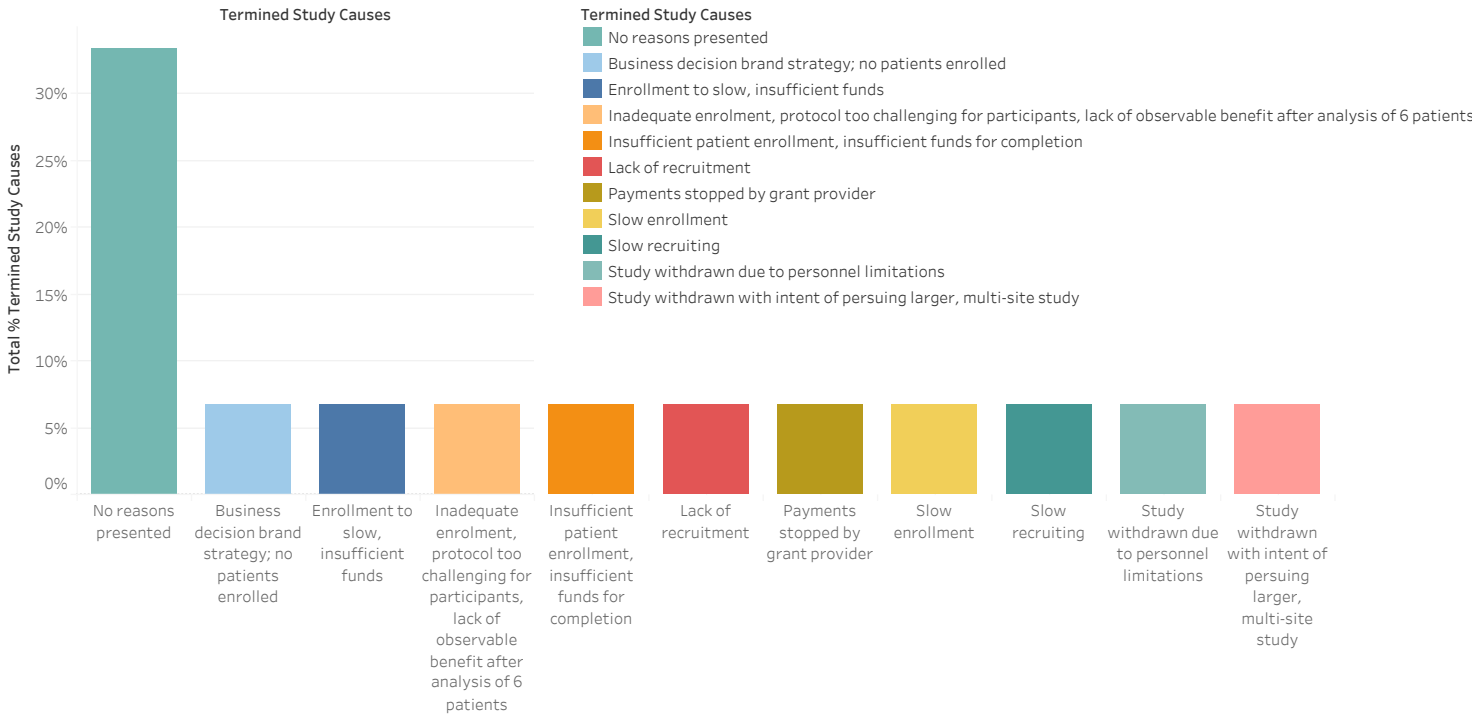


Figure 81. Failure Causes On 4th Phase Of Development Trials
Each color represents a reason for failing confirmatory trials.
The total % studies terminating by the causes listed are presented.

5. The 20 Years Of PubMed PD Publications

To evaluate the discrepancy between the available results and the published results of the overall 613 RCT, the *PDCardPublications* Database was created. For that purpose, the following variables were extracted from PDCard Database: Identification Number, Drug API, Funded By, URL and Study Results Available. Afterwards, the following variables were created : Published in PubMed, Quantity, Publication [1;5].

A filter was created in the Study Results Available (Has results = Yes) and 183 studies were extracted.

For each of the 183 RCT, a research in the 3 RCT databases (*clinicaltrials.gov*, World Health Organization (WHO) International Clinical Trials Search Portal (ICTRP) and Australian New Zealand Clinical Trials Registry (ANZCTR)) was made in order to verify which studies also presented publications referenced/indexed in PubMed. A binary variable was created : Published in PubMed (Yes/No), containing the results of this research. Furthermore, two other variables were created : Quantity, counting the number of publications for each study and Publication [1;5], a string variable with the APA reference of the publication.

A filter was then applied in the Published in PubMed (Yes) and 63 RCT were found (**Figure 82**). That is, 34,4% of the RCT with results, but only 10,20% of the total 613 RCT.

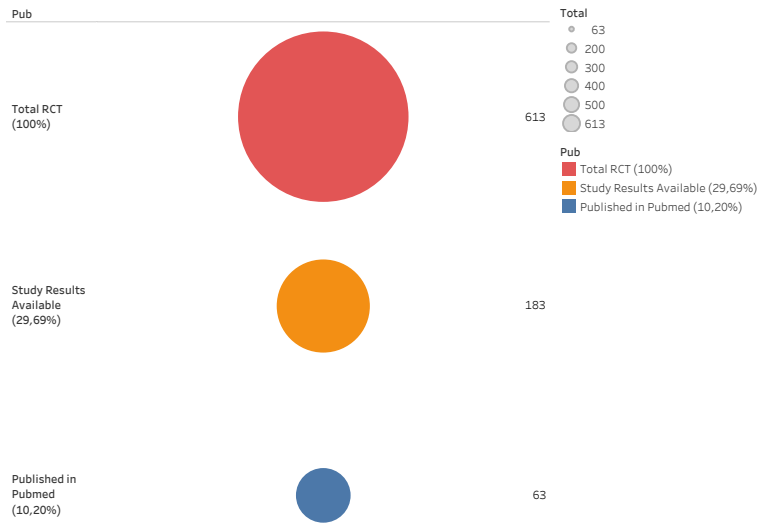


Figure 82. Ratio (RCT/Study Results Available/PubMed)
The discrepancy between the available results and the published results of the overall 613 RCT is presented. Three databases were used. Two sets of selection criteria were applied: (Has Results) and published in PubMed (Yes). The color shows the type of results (red to total RCT; orange to RCT with study results available; and blue to published in PubMed. The size of the circles is referent the total percentage of the 613 RCT.

5.1. RCT Study Results: Registry Of The Protocol And Final Results Obtained

One of the remarks that should be carefully taken into account is that there is a difference between the registry of the protocol of a RCT and the obtained final results that were obtained. On the one hand, a protocol may be amended, and on the other hand, the final results that are obtained might be other than what was foreseen by the protocol when registered. Different versions of the protocol may be registered, because of different reasons, as previously referred in Introduction, but also in Results (failed funds, lack of efficacy or safety, insufficient enrollment, etc.).

5.2. *PDCardPublications* Database: Published And Indexed In PubMed

A total number of 82 publications were found, as some RCT published 2, 3, 4 or 5 publications in PubMed, cf. *PDCardPublications* Database and **Figure 83**. 84,13% of the RCT published 1 article in PubMed, 6,35% of the RCT published 2 articles, 6,35% of the RCT published 3 articles, 1,59% of the RCT published 4 articles, and 1,59% of the RCT published 5 articles.

Quantity	
1	84,13%
2	6,35%
3	6,35%
4	1,59%
5	1,59%

Figure 83. Quantity [1;5] Of Publications In PubMed (By RCT)
The total percentage of the number of PubMed publications by each RCT is presented. The dataset was filtered published in PubMed (Yes). Sixty-three clinical trials were selected.

Finally, the *PDCardPublications* Database, an embedded type database, was published in a secured online server : https://tinyurl.com/PDCardPublications, reviewing the overall panorama of the PubMed publications of the 613 RCT in the last 20 years of PD registered trials.

As a final remark, the study results are not directly published in PubMed. As shown, only a little percentage, i.e. 10,2%, of the RCT effectively publishes theirs results in indexed databases. One of the reasons is that the majority of the results are kept inside the RCT and not directly available, neither published.

5.3. Drug development: Published APIs And Funding

Taken into account the last 20 years of PD drug development, and has shown in **Figure 84**, the API that was more published in PubMed in was Rotigotine, counting 14 publications, followed by Levodopa/Carbidopa, Preladenant and Rasagiline, counting 6 publications, then Ropinirole with 5 publications. The other APIs, in **Figure 84**, published 2 or 1 publications.

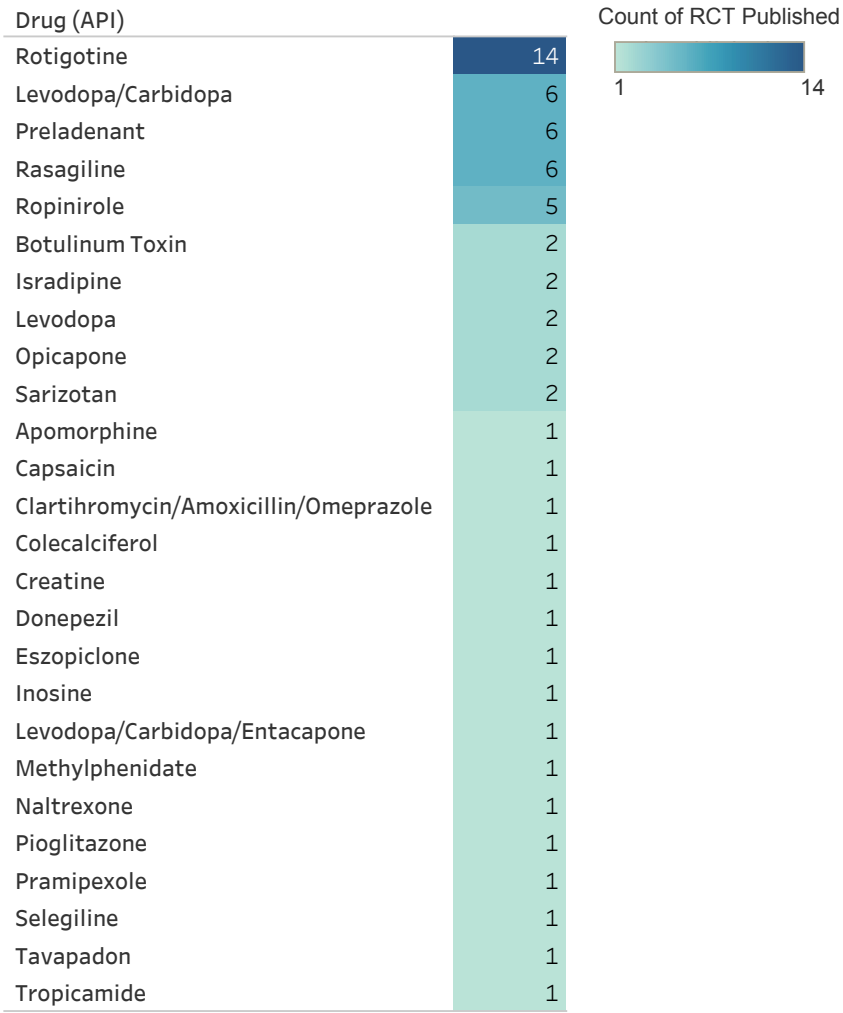


Figure 84. RCT Published In PubMed By API
The number of publications in PubMed by each API is presented.
The gradient of the color is proportional to the number of publications.
Six hundred and thirteen final clinical trials were selected.

These total 82 publications were mainly funded (Figure D), by the industry (69,84%). The NIH in collaborations with other sponsorized entities, other than the industry, published 4,76% of the studies published in PubMed in the last 20 years of PD drug development.

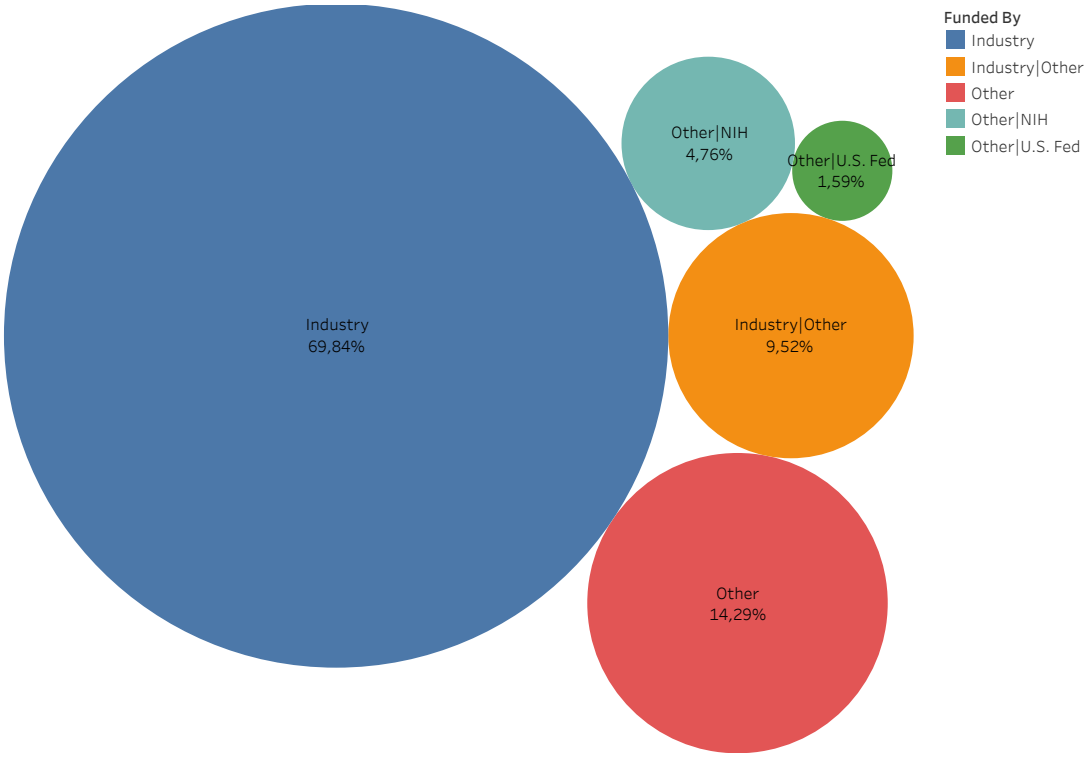


Figure 85. Funding The RCTs Published In PubMed
The total percentage of the RCTs publishing in PubMed are sorted by the type of funding: Industry (blue), Industry|Other (orange), Other (red), Other|NIH (light blue) and Other|U.S. Fed (green).
The size of the circles is correspondent to the total percentage of the sixty-three selected RCT.

Conclusion

This thesis analyzed the data of PD drug development studies registered between 2000 and August 2019. This data is published in the PDCard Database and then described and explored in order to fully explore the success and failure paths. PDCard Database is the knowledge base of the 613 clinical trials, registered in the past 20 years. The descriptive analysis conducted the investigation of those studies and produced 50 independent variables. The exploratory analysis of the success and failure cases presented the rates and causes of success/failure of the 613 clinical trials and the paths of the 187 tested compounds, in 77496 total participants.

In PDCard Database the variables were (i) categorized (ii) systemized and (iii) organized, based on the SPIRIT guidelines. Each of the variables was added manually and extracted from the original publication of the clinical trial or the clinicaltrials.gov, WHO ICTRP and ANZCTR databases.

The clinical trials sample is extracted in majority by the clinicaltrials.gov database, totaling 543 studies, the WHO_ICTRP then provided 67 clinical trials and the ANZCTR provided 3 completed studies that were not present in the other two databases. The 613 clinical trials were financed. Bial funded 34,67% of all PD studies from 1998 to 2019. UCB Pharma funded 13,33, while Boehringer Ingelbeim funded 12,00%. NINDS and NIHCC funded 34,88% of all non-industry PD. One hundred and eighty-four studies were only based in the US. The database includes 115 clinical trials in phase 1, 23 clinical trials in phase 1 and 2, 194 clinical trials in phase 2, 19 clinical trials in phase 2 and 3, 172 clinical trials in phase 3 and 90 clinical trials in phase 4.

42,90% were multicentered studies, while only 13,38% are monocentered. In phase 1, monocentered design is preferred. In phase 1|2, phase 2, phase 2|3, phase 3 and phase 4, multicentered designs are preferred. 74.55% of the studies were randomized and 9,79% are non-randomized studies. 66,72% of the studies are blinded, and that 29,69% are unblinded.

67,86% are completed studies, 11,91% are studies in recruiting phase, 9,62% are studies that are not recruiting, 8,16% are terminated studies and 2,45% are withdrawn studies. From all the terminated study causes of all studies, in phase 1 the more important were first milestone was not met or technical issues with the infusion system. In phase 2, lack of efficiency was the primary cause. In phase 2|3, the main reason was that it was unlikely to provide evidence of significant effect. In phase 3, lack of efficacy and new safety information were the main reasons for terminating the study.

The majority of the studies have recruited adult or older adult subjects, 79,93%. And 12,72% of clinical trials studies are considering only PD subjects in Early-Stage. 12,40 % of clinical trials studies are considered only PD subjects in Advance-Stage. Only 10.77% of clinical trials studies included healthy subjects.

In this study, most of the diseases studied in clinical trials are diseases of the nervous system (IV), totaling 265 studies. Otherwise, 264 of the clinical trials were studying the efficacy and safety of the drug itself, without specifying PD as a condition to the study. Twenty-nine clinical trials studied a sample of subjects with only a mental and behavioral disorders. Nineteen clinical trials studied a sample of subjects with only disease of the digestive system.

The majority of the trials are designed for treatment purpose. Being a minority, the prevention studies are mostly located in phase 2, 3 and 4. Efficacy is the predominating gold at all phases of development in the study population. Safety is the second gold designated in all phases, except in phase 4. Tolerability studies were modestly represented and dose finding studies were the least represented in PDCard Database.

From phase 1 to phase 2, the success rate is 40% and the failure rate is 60%. From phase 2 and 1|2 to phase 3, the success rate is 20% and the failure rate is 60%. From phase 3 and 2|3 to phase 4, the success rate is 29% and the failure rate is 71%. From phase 4 to full approval and complete postmarketing surveillance, the success rate is 83% and the failure rate is 17%.

The success rate is maximum in the completion of phase 4, i.e. PMS, and is minimum in the transition of the API from phase 2 and 1|2 to phase 3. Consequently, the failure rate is maximum in the transition of the API from phase 2 and 1|2 to phase 3, and minimum in phase 4 postmarketing surveillance.

In conclusion, 613 clinical trials in PD conducted from 1998 to 2019, 187 compounds were vastly studies. From these 187 molecules, only 29 were finally licensed compounds that passed confirmatory trials. An absolute success rate in this period was 16% and failure rate was 84%, and those 29 received NDA approvals.

Furthermore, an exploratory analysis was then conducted in the 29 licensed compounds (antiparkinsonians and non-parkinsonians) that completed postmarketing surveillance and received the full approval by the regulatory authorities, but also in the thirty-five compounds that failed to succeed phase 3, i.e. licensing, and in six compounds that failed to succeed phase 4, i.e. PMS.

To finance these 29 compounds, an important funding was provided by different sponsors. Donepezil was single funded, i.e. by the National Institute of Neurological Disorders and Stroke (NINDS). Levodopa was funded by different sponsors, i.e. by the IRCCS San Raffaele, by the Agenzia Italiana del Farmaco, by the University Hospital of Akershus and Solvay Pharmaceuticals. Pramipexole was funded by two big pharma, i.e. by Boehringer Ingelheim and Sandoz, in two separate studies which corresponded to 7,018% and 1,754%, respectively, of the total studies that led to licensing in the last 20 years.

Conclusively, Boehringer Ingelheim, Sandoz and GlaxoSmithKline were the big pharma that conducted more studies for the effective approval of molecules in phase 4. Indeed, industry has funded more studies for each API approved individually when compared to non-industry sponsors. In the last 20 years, industry has funded 36 studies in phase 4, which conducted to the full NDA approval and complete PMS of 18 different molecules. Whilst, only 21 studies were conducted by non-industry sponsors leading to the approval of 18 different compounds. Rasagiline was the compound that was more studies by both types of sponsors.

From all the 29 compounds that were tested in the exploratory analysis, 12 were considered new molecular entities. The new molecular entities that were more studied were rasagiline (30,77%), followed by rotigotine, ropinirole and pramipexole. As previously referred in the Introduction, PD drug development is known as non-informative, but mainly in early-stage trials. Indeed, this tendency is also observed in phase 4, but with less impact.

Moreover, from all the 29 compounds analyzed, 75,44% were tested in a sample of subjects with all stages of PD. Those were the studies that produced more NDA approved compounds and that were more effective. Another factor of success was the type of masking used. Clinical trials that used quadruple blinding (47,22%) are the ones that produced more approved and marketed compounds, followed by double blinding (38,89%), in the last 20 years of PD clinical drug development. Likewise, the type of design used is also a cause of success or failure. The parallel assignment (59,65%) was the type of design that produced licensed compounds, completing PMS, followed by single group assignment (26,32%) and crossover assignment (12,28%).

Other identified causes of success in PD drug development was related to drug administration. The studies that used oral (76,79%) as a preferred route of administration licensed more compounds, followed by transdermal (10,71%), and tailed by intraduodenal and intravenous, with 5,36% each. The studies that used tablets (76,79%) as a preferred drug formulation licensed more compounds, followed by patch (10,71%), and tailed by gel and solution, with 5,36% each. The studies that used solid units (76,79%) as a preferred administration type licensed more compounds, followed by infusion (16,07%), and tailed by injection, with 5,36%.

The 29 licensed compounds that passed all confirmatory trials, including PMS, had different drug modulation mechanisms. Dopamine receptor modulators, like pure levodopa and levodopa combinations, represent 52,63% of the success path in the last 20 years. In second, came monoamine oxidase modulators (19,30%), like selegiline and rasagiline. Thirdly, adrenergic receptor modulators (5,26%), like droxidopa and mirabegron, and catechol o-methyltransferase modulators (5,26%), like entacapone and opicapone, were approved by the regulatory authorities. Approved NDA compounds that were specifically designed to treat PD symptoms have a higher success rate.

From the 29 licensed compounds that passed all confirmatory trials, including PMS, 26,32% of the studies conducted were for non-parkinsonians drugs, while 73,68% of the studies conducted were for antiparkinsonians.

Antiparkinsonian agents are licensed compounds specifically developed and designed for the treatment of PD. Their aim is to replace dopamine either by drugs that release dopamine or those that mimic the action of dopamine. Parkinson's disease is a degenerative disorder of movement that occurs due to dopamine deficiency in the basal ganglia. Antiparkinsonian agents attempt to replace dopamine and treat or halt the symptoms such as tremor, hypokinesia, and so on.

In the past 20 years, 15 antiparkinsonian agents showed regulatory proof and started preregistration to licensing. In the case of PD, the success rate was 29% and they applied later to NDA. Then, they received full NDA approval and regulatory license to marketing. After NDA process, only 12 APIs were preregistered for PD: amantadine, apomorphine, carbidopa/levodopa, levodopa, levodopa/carbidopa/entacapone, opicapone, pramipexole, rasagiline, rivastigmine, ropinirole, rotigotine and safinamide. They all completed successfully the postmarketing surveillance studies, except for safinamide that did not undergo yet postmarketing surveillance studies and rivastigmine that is undergoing a phase 4 trial that started in 2019.

Selegiline, in August 2008, and Entacapone, in November 2009, received full NDA approval and regulatory licensing to market while already in final phase 4 postmarketing surveillance completion.

Finally, from the 613 clinical trials in PD conducted from 1998 to August 2019 and the 187 compounds only 14 APIs were finally licensed antiparkinsonians agents passing the complete development program.

Our results to our main research question showed that the antiparkinsonian success rate is equal to 7%, and the antiparkinsonian failure rate is equal to 93%. The successful antiparkinsonian agents are amantadine, apomorphine, carbidopa/levodopa, levodopa, levodopa/carbidopa/entacapone, entacapone, opicapone, pramipexole, rasagiline, rivastigmine, ropinirole, rotigotine, safinamide and selegiline.

Those 14 different antiparkinsonian agents were marketed by 16 different sponsors, and in 20 different formulations. Novartis was one of the big pharma licensing more compounds (Exelon®, Rivastigmine Tartrate; and Comtan®, Entacapone).

The successful paths started in 1997, the year that selegiline, Requip® (ropinirole hydrochloride) and Mirapex® (pramipexole) were licensed. Presently in 2020, Ongentys® (opicapone) was licensed for the adjunctive treatment to levodopa/carbidopa in PD patients with "off" episodes; and Kynmobi® (apomorphine hydrochloride) was licensed for the treatment of acute and intermittent "off" episodes.

Contrasting the success paths, the failure paths in the last 20 years were due to different reasons. Thirty-five compounds failed to succeed phase 3 (licensing), and six compounds failed to succeed phase 4 (PMS).

In phase 3, lack of efficacy (15%), change of study design (10%) and new safety information (10%) were the main causes for terminating the trials and not being licensed. Some studies that failed to receive regulatory proof (15%) do not publish the reasons for terminating or withdrawing the clinical trial in phase 3.

In phase 4, the majority of studies that failed the confirmatory trials (34%) did not publish the reasons for terminating or withdrawing the clinical trial. The compounds failing PMS were due to the reasons related to business decision brand strategy, slow enrollment, insufficient funds, to the protocol being too challenging for participants, the lack of observable benefit after analysis of patients, or the payments stopped by grant provider.

Outcomes

The overall study was conducted as part of a master program in neuroscience (Faculty of Medicine) under the Mind-Brain College, University of Lisbon, Portugal. The supervisor of this master thesis is Professor Doutor Joaquim Ferreira, Professor of Neurology and Clinical Pharmacology at the Faculty of Medicine, University of Lisbon and Head of the Laboratory of Clinical Pharmacology and Therapeutics; and currently the past-chair of the European Section of the International Parkinson and Movement Disorder Society.

The thesis reviewed the state of the art of clinical drug development in Parkinson's Disease clinical trials from 1998 to 2019. The problematic of exploring the causes for success/unsuccess is a trending topic in neuroscience.

The question raised by this master thesis is if it is possible to better explore the causes to success and to failure in clinical drug development in PD. It is a strategy that is already used by Bouça-Machado and colleagues (2017) and Travessa and colleagues (2017), but to the study clinical trials in palliative care and clinical trials in Huntington's disease. To complete this study limitations, a future and further continuation of the project in *a PhD* is foreseen. For instance, this strategy can be expanded to also study preclinical, diagnosis and non-interventional studies.

Fundamentally, the work of this dissertation responded to the initially defined objectives and the methodology of the master's was significantly put to test. It is then expected that this work will lead to new and interesting questions, which might justify a future study where a multivariate analysis of the 50 variables studied in this master thesis.

We hope we were able to show the landscape of PD therapeutic development programs and critically appraised the causes of compound attrition in the distinct stages of drug development, from phase 1 to phase 4 in Parkinson Disease's studies.

Indeed, there is a high percentage of drug development failures, and a decrease in the number of licensed compounds in the last two decades. Moreover, failures in drug development are observed in all phases of drug development including late stages but are related with non-informative early stage trials.

The main outcome of this methodology is then achieved. It was identified several reasons for development drug failure. Two paths were compared: a successful path with a success rate of 16%, that allowed the licensing and completion of postmarketing surveillance of 29 compounds and a failure path with a failure rate of 84%, that led to the suspension of 158 compounds before the final phase of the development program. Compounds that were still under development preclinical or diagnostic studies were not included in this study.

From those 29 compounds, only 14 are licensed as antiparkinsonian specific agents. Our results showed that, indeed, a final antiparkinsonian success rate is equal to 7%, and the antiparkinsonian failure rate is equal to 93%.

Limitations

This study suffices mainly and only for its methodological account, i.e. the descriptive analysis of the PDCard Database and exploratory analysis of the success and failure paths of 187 compounds tested in the past 20 years. The theoretical account and the hypotheses explored in this descriptive research clearly require further investigation.

The biggest limitation of this work is that it did not provide inferential analysis between the variables studied, neither an exploratory data analysis to better identify which were the variables that most contributed to the success and failure rates on each study phase.

Nevertheless, and in spite of the limitations of this kind of research, it made it possible to advance with a better characterization of PD Clinical Trials.

Statistical analyses should be performed using the Statistical Package of Social Sciences version 20.0.0 (SPSS Inc., Chicago, IL, USA) to conduct an inferential analysis on a set of defined groups in PD drug development. Therefore, a set of chosen variables, yet to be defined, should then be used to better determine evidence. Thus, evidence of the failure of components in the various phases and of those who have not received regulatory approval should be better investigated and detailed.

In order not to exceed the findings and to be consistent with the objectives, the conclusions of this dissertation are presented exclusively in relation to the primary hypothesis raised.

Another limitation of this study analysis is the confidence and generalization of the success phases rate. Our study only considered interventional studies with the primary purposed being treatment or prevention. Observational, basic science, cause and cohort studies are excluded, as well as studies with diagnostic, research, screening and supportive care purposes. Trials with a non-drug aim, like behavioral, biological (not drug associated), device, procedure, radiation or genetic based studies were also excluded. All the trials conditions not based on diagnosis code G20 or with study status “not yet recruiting” are excluded. All these variables, and the way that it can importantly transform the success phase rate, will be interesting to explore on a future study. The time of such a study was an important limitation for its development in a master thesis framework.

Considering the limitations mentioned, the resulting work was achieved, and the following outcomes were attained.

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