Dr. Gabrielle Page-Wilson

Project Summary/Abstract
Prolactinomas are the most commonly occurring secretory pituitary tumors. They routinely result in clinical symptoms including hypogonadism, infertility, low bone density and galactorrhea and in the setting of macroprolactinomas can be associated with hypopituitarism and neurologic manifestations like headaches and vision loss. The ergot dopamine agonists (DA), cabergoline and bromocriptine, have been shown to lower PRL levels and promote tumor shrinkage, and are currently standard therapy for the treatment of prolactinomas, however drug intolerance and resistance are observed in a subset of patients. Additionally, the ergot DAs lack specificity for the dopamine D2-receptor subfamily and exhibit cross-reactivity at other receptors, including the 5HT-2B receptor expressed on heart valves, increasing the risk of cardiac valve disease and impacting tolerability. In the case of Parkinson's disease, due to the recent emergence of data highlighting an association between ergoline DAs and valvular heart disease, the newer safer non-ergot DAs, like ropinirole and pramipexole, have replaced the ergot derivatives as preferred therapy. To date, the utilization of non-ergot DAs in the treatment of prolactinomas has not been studied. However, the more D2/D3 selective non-ergot DA ropinirole, which has negligible activity at other receptors, has been shown to lower PRL levels in Parkinson's patients and in healthy volunteers without major side effects. Although FDA approved solely for the treatment of Parkinson's and Restless Leg Syndrome, our preliminary data highlight ropinirole's potential as a novel therapy for the treatment of prolactinomas with an improved tolerability and risk profile. Capitalizing on the rich patient resources of our Neuroendocrine Unit, the objective of this proposal is to determine, for the first time, if the non-ergot DA ropinirole effectively and tolerably lowers PRL levels, restores gonadal function, and induces tumor shrinkage in individuals with prolactinomas. By carrying out a 24-hour forced titration dose-response study of ropinirole's effect on PRL concentrations, we aim to establish the pharmacodynamic and pharmacokinetic profile of this drug in prolactinoma patients. We also aim to determine the long-term efficacy and tolerability of ropinirole for the treatment of prolactinomas by conducting a prospective Phase II 24-week dose escalation trial. We anticipate that ropinirole will effectively and tolerably suppress PRL levels, improve gonadal function, and reduce tumor size in this population. Ultimately, the execution of these aims has the potential to bring forth a pragmatic pharmacologic alternative for the treatment of prolactinomas that will expand our therapeutic arsenal and offer a new treatment option to patients with pre-existing cardiac valve disease as well to those with pharmacologic resistance or intolerance to traditional medications, thereby improving the current clinical standard of care.