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Dear Dr,

William is currently experiencing low mood and anxiety despite therapy. He has sought out a consultation with a clinical pharmacist. This consultation included a pharmacogenetic test.

According to William's pharmacogenetic test and medication history, we recommend:

- The continuation of Bupropion (Wellbutrin XL) 300 mg along with the potential initiation of Sertraline (Zoloft) 25 mg once daily titrated to effect

SUMMARY:

Low Likelihood of Response and/or High Risk of Side-Effects:

- **Antipsychotics** (i.e. Abilify, Rexulti, etc.)
- **Certain Tricyclic Antidepressants** (i.e. Amitriptyline, Clomipramine, Imipramine, Trimipramine)
- **Fluoxetine** (Prozac)
- **Fluvoxamine** (Luvox)
- **Paroxetine** (Paxil)
- **Venlafaxine** (Effexor)
- **Desvenlafaxine** (Pristiq)

Moderate Response:

- **Citalopram** (Celexa)
- **Escitalopram** (Cipralex)
- **Fluvoxamine** (Luvox)
- **Venlafaxine** (Effexor)
- **Desvenlafaxine** (Pristiq)

High Likelihood of Response:

- **Bupropion** (Wellbutrin)
- **- Sertraline** (Zoloft)

Rationale:

According to a high level of evidence, William is a CYP2C19 *1/*1 normal metabolizer of Citalopram, Escitalopram, Certain Tricyclic Antidepressants, and Sertraline. This means that he clears these medications at a normal rate and is able to maintain sufficient levels in his body for therapeutic effect. However, according to lower level evidence (*see Supplementary Table*), tested serotonin and brain receptor genes indicate a low likelihood of response to Citalopram and Escitalopram (~43%) along with a risk of memory and concentration problems (i.e. brain fog) as per serotonin receptor gene **HTR2A rs6311 CT**. In contrast, tested genes indicate a high likelihood of response to Sertraline (>95%). This medication is generally well tolerated with a

low risk of drug interactions. We thus recommend the initiation of this medication. If a Tricyclic antidepressant is warranted, consider Desipramine/Nortriptyline as they are not metabolized by CYP2C19, and they have the lowest risk of anticholinergic side-effects (i.e. concentration problems and urinary retention).

According to a high level of evidence, William is a CYP2D6 *1/*2 normal metabolizer of Fluoxetine, Fluvoxamine, Paroxetine, and Venlafaxine. This means he is able to clear these medications from his body at a normal rate and maintain sufficient levels for therapeutic effect. Caution should these medications be combined with Bupropion, as Bupropion is able to inhibit the CYP2D6 pathway resulting in slight accumulation and increased sensitivity to adverse effects. However, according to lower level evidence (*see Supplementary Table*) tested brain receptor/transporter genes indicate a low likelihood of response on Fluoxetine (~14%), Paroxetine (50%), Venlafaxine/Desvenlafaxine (50%) and only a moderate likelihood of response to Fluvoxamine (~67%). In terms of side-effects, William is at risk of insomnia on Fluoxetine (**BDNF rs6265 CC**), stomach upset and nausea on Fluvoxamine (**HTR2A rs6311 CT**) and dose-related anxiety and fatigue on Venlafaxine/Desvenlafaxine (**DRD2 rs1800497 GG** and **COMT rs4680 GA**). Though there is scarce genetic data regarding Vortioxetine, this medication is also likely to cause an upset stomach.

According to a high level of evidence, William has a high likelihood of response to Bupropion as per the tested dopamine receptor genes (DRD2/ANNK1 rs1800497 GG and rs1799732 GG). This has been extrapolated from randomized controlled trials and meta-analysis of smoking cessation studies, given similar dopaminergic pathways are implicated in depression. However, Bupropion treats depression and not anxiety. For patients with anxiety, it is important that an SSRI is added as adjunctive therapy. William showed the highest likelihood of response to SSRI Sertraline (>95%). We thus recommend the addition of SSRI Sertraline 25 mg once daily titrated to effect if required. Bupropion helps to improve mood and energy through raising levels of dopamine and norepinephrine (noradrenaline) which is an activating neurotransmitter, whereas serotonin activity in Sertraline helps to mitigate anxiety. Sertraline also has some weak affinity for dopamine and will work in synergy with Bupropion.

According to moderate level evidence, William is at risk of movement disorders on antipsychotics, as per the tested genes (DRD2/ANNK1, HTR2A, COMT, and HSPG2). William is particularly at risk of dose-related akathisia (motor restlessness) on Aripiprazole (Abilify) and Brexpiprazole (Rexulti). This side-effect can manifest as a feeling of inner restlessness, an inability to sit still (i.e. pacing) and a sense of anxiety. William is also at risk of raised blood pressure and blood sugar levels on these medications as per **COMT rs4680 GA**.

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Supplementary Table: Brain Receptor/Transporter Genes Tested. *With a few exceptions (i.e. DRD2 and Bupropion), the evidence associating one brain receptor/transporter gene with response is weak. We thus looked at multiple genes to help guide therapy. This information can be useful when combined with physician monitoring of response.*

Serotonin	Dopamine	Norepinephrine	HPA Axis	Other:
HTR1A **rs10042486 TT** **rs6295 GG** **HTR2A** **rs7997012 GA** **rs6311 CT** **rs6313 GA** **HTR2C** **rs1414334 GG** **TPH1** **rs1800532 GT**	**DRD1** **rs4532 CT** **DRD2/ANNK1** **rs1800497 GG** **rs1799732 GG** **DRD3** **rs6280 TT** **COMT** **rs4680 GA**	**ADRA2A** **rs1800544 CC** **COMT** **rs4680 GA**	**BDNF** **rs6265 CC** **FKBP5** **rs4713916 GA** **GRIK4** **rs1954787 TT** **MC4R** **rs17782313 TT**	**ABCB1/PgP** **rs2032583 AG** **rs1045642 GA** **HSPG2** **rs2445142 GG** **CNR1** **rs1049353 CC** **FAAH** **rs324420 CC** **MTHFR** **rs1801133 GA**

Other untested clinical and genetic factors can also affect response. Patient has been informed to follow-up with the physician prior to making any changes to his medications.

References:

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Feel free to contact me, if you have any questions.
Thanks in advance.
Regards,

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